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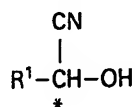
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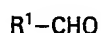
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None(58) Field of search
C2C(54) Process for the preparation of α -substituted α -cyanomethyl alcohol enantiomers(57) A process for the preparation of an α -substituted- α -cyanomethyl alcohol enantiomer of formula I

I

wherein the group R^1 is an optionally substituted alkenyl, alkynyl, aryl or heteroaryl group comprises reacting an aldehyde of formula II



II

with hydrogen cyanide in the presence of a cyclic dipeptide enantiomer at a temperature below ambient, and enables the preparation of compounds of formula I in high yield and high enantiomeric excess. The enantiomers of formula I may be used as intermediates for the preparation of chiral pyrethroids by esterification and chiral aryethanolamines, by reduction.

A cyclic dipeptide enantiomer comprising (R)-histidine or a derivative thereof, and also certain substituted benzaldehyde cyanohydrins are claimed per se.

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SPECIFICATION

Asymmetric synthesis of α -substituted- α -cyanomethyl alcohols

- 5 This invention relates to a process for the asymmetric synthesis of α -substituted- α -cyanomethyl alcohols and the use of such alcohols as intermediates in the preparation of chiral esters and chiral ethanolamines and in particular chiral pyrethroids and chiral arylethanolamines. 5

It is known in the art that in pyrethroids of general formula



- 15 for a given pyrethrin acid or pyrethroid acid moiety JCO— and a given pyrethroid alcohol moiety $\text{R}^1-\text{CH}(\text{CN})\text{O}-$, there is a wide variation in pesticidal activity between the two pyrethroid isomers prepared from the two alcohol enantiomers (* indicates a chiral centre). Therefore, there is considerable interest in the art in the development of methods for preparing the individual pyrethroid alcohol enantiomers and their use in the preparation of the more pesticidally active pyrethroid isomer. 15

- 20 A preferred method for preparing the individual pyrethroid alcohol enantiomers would be a synthesis which gave an enantiomer in substantially pure form. However, hitherto there has been no publication of an asymmetric synthesis of individual pyrethroid alcohol enantiomers. All methods for the preparation of individual pyrethroid alcohol enantiomers which have been described hitherto have involved the resolution of the racemic mixture of alcohols or derivatives thereof. For example, in United Kingdom Patent Application 25 No 2 013 670A there is disclosed a process for the preparation of the pyrethroid alcohol (S)- α -cyano-3-phenoxybenzyl alcohol. The preparation involves a resolution process in which the racemic alcohol is reacted with an optically active lactone to give a mixture of the two diastereomeric ethers of the alcohol enantiomers, the diastereomeric ethers are separated by chromatography over silica gel and the ether of the (S)-alcohol is hydrolysed under acid conditions to give (S)- α -cyano-3-phenoxybenzyl alcohol 30 which is purified by chromatography over silica gel. Clearly this is a long and costly process which, although suitable for small scale laboratory preparations, would prove difficult to adapt for large scale commercial manufacture. 30

- It is known in the art that the naturally occurring physiologically active arylethanolamine norepinephrine (noradrenaline) is in the laevorotatory optically active form which has the absolute configuration (R) at the 35 chiral centre. Many synthetic arylethanolamines have been prepared which are physiologically active by virtue of binding at norepinephrine receptor sites but to date all of their syntheses have involved the preparation of the racemic arylethanolamines. 35

- In view of the difficulty in resolving the racemic mixtures of the sympathomimetic arylethanolamines, the commercially available pharmaceutical preparations containing these compounds have to date generally 40 contained the racemic arylethanolamine. However, it has been found that S-isomer or dextrorotatory optical isomer of these compounds may have some undesired effects. Therefore, clearly it would be advantageous to be able to synthesise the R-isomer of these arylethanolamines to give products more like the naturally occurring norepinephrine and hence products having a more selective action, a greater therapeutic ratio and more cost-effectiveness. 40

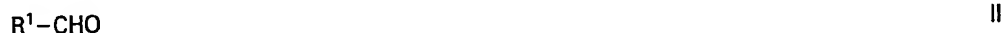
- 45 In a recent paper Ohu, Ito and Inoue (Makromol. Chem. 183, 579-586 (1982) disclosed a process for the asymmetric synthesis of cyanohydrins using synthetic dipeptides. In this paper there is described the reaction of benzaldehyde with hydrogen cyanide in the presence of a synthetic dipeptide to give α -cyanobenzyl alcohol. The paper reports that in the early stage of the reaction the addition was highly stereospecific but the product isolated comprised a mixture of enantiomers with an enantiomeric excess 50 only of the order of 0.1 to 10.1%. The conclusion drawn in the paper was that the catalyst racemized the product and that the process would be suitable for asymmetric cyanohydrin synthesis "if a procedure is established to separate the product rapidly from the catalyst before the catalysed racemization takes place". 50

- It has now been found that α -substituted α -cyanomethyl alcohol enantiomers can be prepared in a highly stereospecific reaction by the asymmetric addition of hydrogen cyanide to aldehydes in the presence of a 55 cyclic dipeptide catalyst without rapid separation of the product from the catalyst and that the product α -substituted- α -cyanomethyl alcohols comprise either substantially one enantiomer or a high proportion (typically 75 to 100%; ie 50 to 100% enantiomeric excess) of one enantiomer which may be used in the preparation of pyrethroid enantiomers and arylethanolamine enantiomers. 55

Accordingly the invention provides a process for the preparation of an α -substituted- α -cyanomethyl alcohol enantiomer of formula I



wherein the group R^1 is an alkenyl, alkynyl, aryl or heteroaryl group; which process comprises reacting an aldehyde of formula II

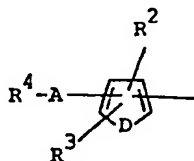


with hydrogen cyanide in the presence of a cyclic dipeptide enantiomer, and wherein said reaction is carried out at a temperature below ambient temperature.

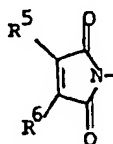
It is to be understood that in the context of this specification the term "enantiomer" is used to refer to a product comprising substantially one enantiomer or a product comprising a high proportion, typically 75% or more and preferably more than 90%, of one enantiomer.

Suitable values for R^1 include groups of the formulae:

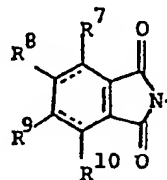
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III

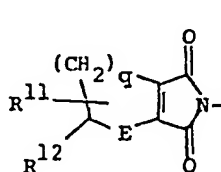


IV

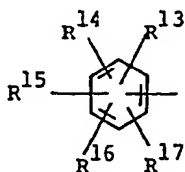


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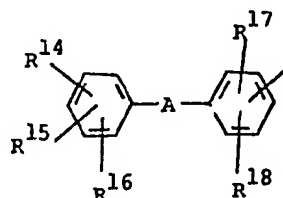
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VI



VII

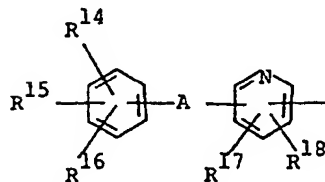


VIII

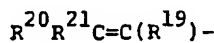
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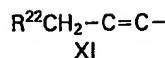
IX



X

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XI

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wherein:

R^2 and R^3 are independently selected from hydrogen, halogen, C_1 to C_6 alkyl and C_1 to C_6 haloalkyl, or R^2 and R^3 jointly form a trimethylene or tetramethylene bridging group;

A is selected from oxygen, sulfur, $-\text{CO}-$ and $-\text{CH}_2-$;

R^4 is selected from hydrogen, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, phenyl, furyl, thienyl and the groups phenyl, furyl and thienyl wherein each group is substituted by halogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxy or C_2 to C_6 alkenyl;

D is selected from oxygen and sulfur;

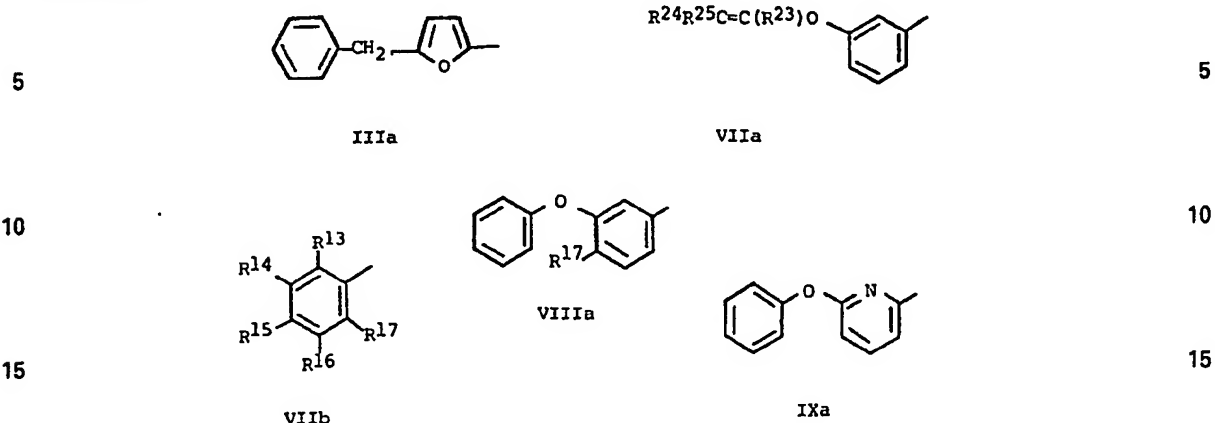
R^5 and R^6 are independently selected from C_1 to C_6 alkyl;

$\text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}$ are independently selected from hydrogen, halogen, and C_1 to C_6 alkyl;

65

- R¹¹ and R¹² are independently selected from hydrogen, C₁ to C₆ alkyl and halogen, or R¹¹ and R¹² jointly form a methylenedioxy bridging group;
 E is selected from oxygen, sulfur and -CH₂-;
 q is an integer selected from 1 and 2;
- 5 R¹³ is selected from the group consisting of hydrogen, halogen, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, thienyloxy, thenyl, furylmethyl and the groups R²⁴R²⁵C=C(R²³)O- and R²⁴R²⁵C=C(R²³)- in which R²³ is selected from hydrogen and C₁ to C₆ alkyl and R²⁴ and R²⁵ are independently selected from hydrogen, halogen, C₁ to C₆ alkyl and C₁ to C₆ haloalkyl;
 R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen, C₁ to C₆ alkyl, halogen and C₂ to C₆ alkenyl;
 R¹⁹ is selected from hydrogen, chlorine and C₁ to C₆ alkyl;
 R²⁰ and R²¹ are independently selected from hydrogen, fluorine, chlorine, bromine, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, phenyl, benzyl, furylmethyl and thienylmethyl; and
 R²² is selected from phenyl, phenoxy and the groups phenyl and phenoxy wherein each group is substituted by halogen, nitro, cyano, C₁ to C₆ alkyl, C₁ to C₆ halo-alkyl or C₁ to C₆ alkoxy.
 Preferred values for R¹ include groups of formulae III, IV, V, VI, VII, VIII, IX, X and XI wherein:
 R² and R³ are independently selected from hydrogen, halogen, C₁ to C₆ alkyl and C₁ to C₆ haloalkyl, or R² and R³ jointly form a trimethylene or tetramethylene bridging group;
 A is selected from oxygen, sulfur, -CO- and -CH₂-;
- 20 R⁴ is selected from hydrogen, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, phenyl, furyl, thienyl and the groups phenyl, furyl and thienyl wherein each group is substituted by halogen, C₁ to C₆ alkyl, C₁ to C₆ alkoxy or C₂ to C₆ alkenyl;
 D is selected from oxygen and sulfur;
 R⁵ and R⁶ are independently selected from C₁ to C₆ alkyl;
- 25 R⁷, R⁸, R⁹ and R¹⁰ are independently selected from hydrogen, halogen, and C₁ to C₆ alkyl;
 R¹¹ and R¹² are independently selected from hydrogen, C₁ to C₆ alkyl and halogen, or R¹¹ and R¹² jointly form a methylenedioxy bridging group;
 E is selected from oxygen, sulfur and -CH₂-;
 q is an integer selected from 1 and 2;
- 30 R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are independently selected from the group consisting of: hydrogen; halogen; nitro; C₁ to C₆ alkyl; C₁ to C₆ haloalkyl; C₁ to C₆ hydroxyalkyl; C₂ to C₆ alkenyl; C₂ to C₆ alkynyl; C₁ to C₆ alkoxy; C₁ to C₆ alkylthio; (C₁ to C₆ alkoxy) carbonyl; benzyloxy, substituted benzyloxy; acyloxy; hydroxy; tri(C₁ to C₆ alkyl)silyloxy; (C₁ to C₆ alkoxy) C₁ to C₆ alkoxy; C₁ to C₆ alkoxy-C₁ to C₆ alkoxy-methoxy; amino; N-(C₁ to C₆ alkyl)amino; N,N-di(C₁ to C₆ alkyl)amino; N-(C₁ to C₆ alkanoyl)amino; N-(C₁ to C₆ alkyl)sulfonyl-amino; N-(benzenesulfonyl)amino; N-(substituted benzene-sulfonyl)amino; ureido; N-[tri(C₁ to C₆ alkyl)silyl]amino; sulfamoyl; N-(C₁ to C₆ alkyl)sulfamoyl; N,N-di(C₁ to C₆ alkyl)-sulfamoyl; carbamoyl; N-(C₁ to C₆ alkyl)carbamoyl; N,N-di(C₁ to C₆ alkyl)carbamoyl; C₁ to C₆ alkylsulfinyl; C₁ to C₆ alkylsulfonyl; thienyloxy; thenyl; furylmethyl; or two adjacent substituents are selected from the linking group buta-1,3-dienylene; and the groups R²⁴R²⁵C=C(R²³)O- and R²⁴R²⁵C=C(R²³)- in which R²³ is selected from hydrogen and C₁ to C₆ alkyl and R²⁴ and R²⁵ are independently selected from hydrogen, halogen, C₁ to C₆ alkyl and C₁ to C₆ haloalkyl;
 R¹⁹ is selected from hydrogen, chlorine and C₁ to C₆ alkyl;
 R²⁰ and R²¹ are independently selected from hydrogen, fluorine, chlorine, bromine, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, phenyl, benzyl, furylmethyl and thienylmethyl; and
 R²² is selected from phenyl, phenoxy and the groups phenyl and phenoxy wherein each group is substituted by halogen, nitro, cyano, C₁ to C₆ alkyl, C₁ to C₆ halo-alkyl or C₁ to C₆ alkoxy.
 When R¹ is a group of formula VIIb and one or more of R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are selected from acyl, suitable acyl groups include C₂ to C₆ alkanoyl, benzoyl and substituted benzoyl.
 When R¹ is a group of formula VIIb and one or more of R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are selected from substituted benzyloxy, substituted benzoyl or N-(substituted benzenesulfonyl)amino, suitable benzene ring substituents include one to three substituents selected from the group consisting of halogen, nitro, cyano, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, C₁ to C₆ alkoxy and C₁ to C₆ alkylthio.

More preferred values for R^1 include groups of formulae III, VII, VIII and IX above and in particular groups of formulae



- 20 wherein:
- in formula VIIIa, R^{17} is selected from hydrogen and halogen;
 - in formula VIIb, R^{13} , R^{14} , R^{15} , R^{16} and R^{17} are independently selected from the group consisting of hydrogen, halogen, nitro, hydroxy, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_1 to C_6 hydroxyalkyl, C_1 to C_6 alkoxy, (C_1 to C_6 alkoxy) C_1 to C_6 alkoxy, amino, N-(C_2 to C_6 alkanoyl)amino, N-(C_1 to C_6 alkylsulfonyl) amino, sulfamoyl, ureido, benzyloxy, benzoyloxy, or two adjacent substituents are selected from the linking group buta-1,3-dienylene; and in formula VIIa, R^{23} is hydrogen and R^{24} and R^{25} are independently selected from hydrogen and halogen.
- Even more preferred values for R^1 include groups of formulae IIIa, VIIa, VIIb and VIIIa wherein;
- in formula VIIIa, R^{17} is selected from hydrogen and fluorine;
 - 30 in formula VIIb, R^{13} , R^{14} , R^{15} , R^{16} and R^{17} are independently selected from the group consisting of hydrogen, halogen, methyl, trifluoromethyl, hydroxymethyl, methoxy, (1-(ethoxy)ethoxy, nitro, amino, acetamido, methanesulfonylamino, sulfamoyl, ureido, benzyloxy, benzoyloxy, or two adjacent substituents are selected from the linking group buta-1,3-dienylene;
 - in formula VIIa, R^{23} is hydrogen and R^{24} and R^{25} are independently selected from hydrogen and halogen.

Specific examples of the compounds of formula I which may be prepared according to the process of the present invention include both the (R)- and (S)- enantiomers of the compounds illustrated in Tables 1 and 2 below.

TABLE 1

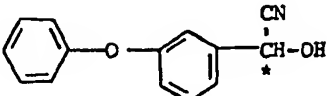
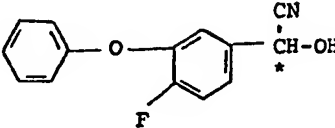
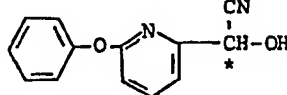
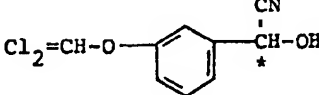
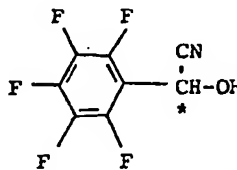
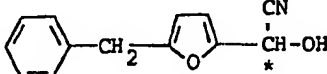
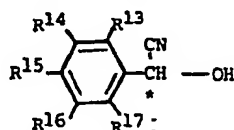
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TABLE 2

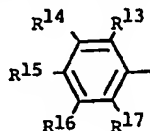


Compound No	R^{13}	R^{14}	Substituents R^{15}	R^{16}	R^{17}
8	H	H	H	H	H
9	H	HO	H	H	H
10	H	HO	HO	H	H
11	H	HO	H	HO	H
12	H	HOCH ₂	HO	H	H
13	H	CH ₂ SO ₂ NH	HO	H	H
14	H	H	HO	H	H
15	H ₂ NCONH	HO	H	H	H
16	H	Cl	H ₂ N	Cl	H
17	Cl	H	H	H	H
18	H	CH ₃ O	HO	CH ₃ O	H
19	H	H ₂ NSO ₂	CH ₃	H	H
20	H	H	NO ₂	H	H
21	H	CH ₃ O	H	H	H
22	H	H	CH ₃ O	H	H
23	H	H	CF ₃	H	H
24	H	-CH=CH-CH=	CH-	H	H
25	H	Cl	H	H	H
26	H	CH ₃ CO	H	H	H
27	H	NO ₂	H	H	H
28	H	a	a	H	H
29	H	a	H	H	H
30	H	H	Cl	H	H
31	H	H	b	H	H
32	H	c	c	H	H
33	H	d	d	H	H
34	H	CH ₃ O	CH ₃ O	H	H
35	CH ₃	H	H	H	H

Code: a - C₆H₅CH₂O
 b - CH₃CONH
 c - C₆H₅COO
 d - CH₃CH₂OCH(CH₃)O

One particularly preferred compound which may be made is high yield and high enantiomeric excess according to the process of the present invention is the (S)-isomer of compound No 1, that is (S)- α -cyano-3-phenoxybenzyl alcohol.

One particularly preferred group of compounds which may be made according to the process of the present invention are the (R)-isomers of compounds of formula I in which R¹ has the formula VIIb



VIIb

wherein;

from one to three of the substituents R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are selected from the group consisting of methoxy, methyl, halogen, hydroxy, nitro, trifluoromethyl, acetyloxy and benzyloxy, or two adjacent substituents are selected from the linking group buta-1,3-dienylene; and the remaining substituents are hydrogen.

In the preparation, according to the process of the present invention, of compounds of formula I in which R¹ is a group of formula VII, VIII or IX wherein one or more of R¹³, R¹⁴, R¹⁵, R¹⁶ or R¹⁷ is a basic or acidic substituent, for example hydroxy or amino, or a substituent with a strong electronic effect, for example nitro

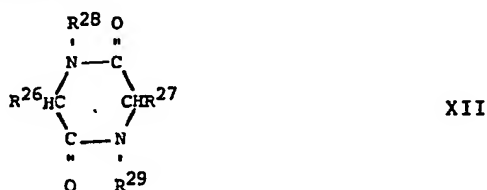
or sulfamoyl, such substituents may adversely affect the rate and/or stereospecificity of the reaction. However, compounds of formula I containing such substituents may be readily prepared according to the process of the present invention by masking or protecting such interfering substituents utilizing masking or protecting groups of the type well known in the art. The process of the present invention may be effected on the compound of formula II having masking or protecting groups and the protecting groups removed from the product to afford the desired compound of formula I.

Suitable masking or protecting groups:

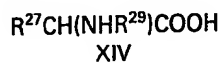
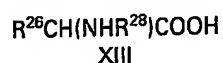
- for hydroxy include C₂ to C₆ carboxyl esters, benzoyl and substituted benzoyl esters, C₁ to C₆ alkyl ethers, benzyl and substituted benzyl ethers, trialkylsilyl ethers, and acetals or ketals formed with C₁ to C₆ aldehydes or C₃ to C₆ ketones and C₁ to C₆ alcohols; for amino and N-(C₁ to C₆ alkyl)amino, include C₂ to C₆ alkanoyl amides, benzoyl and substituted benzoyl amides, C₁ to C₆ alkyl sulfonyl amides, benzenesulfonyl and substituted benzenesulfonyl amides and trialkylsilyl amides;
- for carboxy include C₁ to C₆ alkyl esters and benzyl and substituted benzyl esters;
- for nitro include amides, sulfonamides and silyl amides as indicated above for amino;
- for sulfamoyl, N-(C₁ to C₆ alkyl)sulfamoyl and N,N-di(C₁ to C₆ alkyl)sulfamoyl include thioethers which may be oxidized and reacted with the appropriate amine; and for carbamoyl, N-(C₁ to C₆ alkyl)carbamoyl and N,N-di (C₁ to C₆ alkyl)carbamoyl, include esters, as indicated above for carboxy, which may be reacted with the appropriate amine.

It is to be understood that the process of the present invention includes within its scope the preparation of compounds of formula I having masked or protected substituents by reaction of corresponding compounds of formula II having masked or protected substituents and release of the desired compound of formula I if desired by removal of the masking or protecting group.

Suitable cyclic dipeptide enantiomers which may be used as catalysts in the process of the present invention include diketopiperazines of the formula



which may be prepared by coupling two α-amino acids of formula XIII and XIV wherein R²⁸ and R²⁹ are hydrogen or by coupling two α-amino acid derivatives of formula XIII and XIV wherein R²⁸ and R²⁹ are substituents other than hydrogen.



Suitable amino acids include alanine, cysteine, histidine, homoserine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, serine, threonine, tryptophan, tyrosine, valine and the N-alkyl, N-alkenyl and N-acyl derivatives thereof. Preferably one of the amino acids in the diketopiperazine of formula XII is chosen from histidine, tryptophan or a derivative thereof. Preferably the other amino acid in the diketopiperazine of formula XII is one which has a large or bulky α-substituent. Examples of such amino acids include histidine, phenylalanine, threonine, tyrosine, tryptophan and derivatives thereof.

Examples of diketo-piperazine derivatives include compounds of formula XII wherein R²⁸ and R²⁷ are independently selected from phenyl, benzyl, 4-hydroxybenzyl, 4-benzyloxybenzyl, 4-methoxybenzyl, 4-phenyl, 4-methyl, 4-imidazolylmethyl and 3-indolylmethyl, and R²⁸ and R²⁹ are independently selected from hydrogen, alkyl, alkenyl and acyl. Such compounds include, for example:

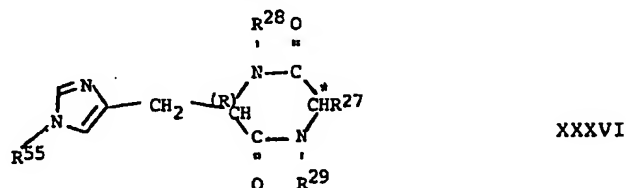
- (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (cyclic (R)-phenylalanyl-(R)-histidine; C.(R)-Phe-(R)-His); (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione (cyclic (S)-phenylalanyl-(S)-histidine; C.(S)-Phe-(S)-His);
- (S)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (cyclic (S)-phenylalanyl-(R)-histidine; C.(S)-Phe-(R)-His); (R)-3-(4-hydroxybenzyl)-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (cyclic (R)-tyrosyl-(R)-histidine; C.(R)-Tyr-(R)-His);
- (R)-3-(4-benzyloxybenzyl)-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (cyclic O-benzyl-(R)-tyrosyl-(R)-histidine; C.O-BZ-(R)-Tyr-(R)-His);
- (R)-3-(4-methoxybenzyl)-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (cyclic O-methyl-(R)-tyrosyl-(R)-histidine; C.O-Me-(R)-Tyr-(R)-His);
- (R)-4-phenyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (cyclic (R)-phenylglycyl-(R)-histidine; C.(R)-Phegly-(R)-His); (R)-4-methyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (cyclic (R)-alanyl-(R)-histidine; C.(R)-Ala-(R)-His); (S),(S)-3,6-bis(4-imidazolylmethyl)-2,5-piperazinedione (cyclic(S)-histidyl-(S)-histidine; C.(S)-His-(S)-His); and (R), (R)-3,6-bis(4-imidazolylmethyl)-2,5-piperazinedione(cyclic (R)-histidyl-(R)-histidine; C.(R)-His-(R)-His).

Preferred cyclic dipeptide enantiomers for use in the process of the present invention include (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (C.(R)-Phe-(R)-His) and (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione (C.(S)-Phe-(S)-His).

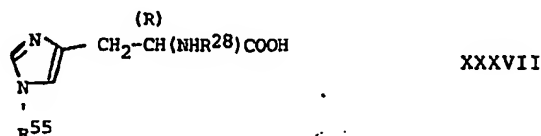
Certain of the cyclic dipeptides which may be used as catalysts in the process of the present invention are novel compounds. For example, certain cyclic dipeptides in which (R)-histidine is one of the amino acid residues and which have been found to be particularly suitable for the preparation of the (S)-isomers of α -substituted- α -cyanomethyl alcohols according to the process of the present invention are novel compounds.

According to a further embodiment the invention provides a cyclic dipeptide enantiomer, comprising (R)-histidine or a derivative thereof as one of the amino acid residues.

The cyclic dipeptide enantiomers of this embodiment of the present invention are diketopiperazines which may be depicted by the following formula XXXVI



and which may be prepared by the coupling of the amino acid (R)-histidine, or a derivative thereof, of formula XXXVII



and an amino acid, or a derivative thereof, of formula XXXVIII



Suitable (R)-histidines of formula II include (R)-histidine and the N-alkyl, N-alkenyl and N-acyl derivatives thereof. That is, for example, compounds of formula II wherein R^{28} and R^{55} are independently selected from hydrogen, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkanoyl and benzoyl. Preferably the amino acid of formula II is (R)-histidine.

Suitable amino acids of formula III include alanine, cysteine, histidine, homoserine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, serine, threonine, tryptophan, tyrosine, valine and the N-alkyl, N-alkenyl and N-acyl derivatives thereof. Preferably the amino acid of formula III is one which has a large or bulky α -substituent. Such amino acids include, for example, histidine, phenylalanine, threonine, tyrosine, tryptophan and derivatives thereof. Phenylalanine is a preferred amino acid of formula XXXVIII.

It is preferred that the amino acids comprising the cyclic dipeptide enantiomer of this embodiment of the present invention have the same stereochemistry. Therefore, the preferred cyclic dipeptide enantiomers comprise (R)-histidine and another (R)-amino acid. A more preferred cyclic dipeptide enantiomer comprises (R)-histidine and (R)-phenylalanine, that is, the compound of formula I in which R^{27} is benzyl, R^{28} , R^{29} and R^{55} are each hydrogen and the asymmetric centre alpha to R^{27} has the (R)-configuration.

The cyclic dipeptide enantiomers of formulae XII and XXXVI may be prepared by standard methods known to those skilled in the art. For example, the cyclic dipeptide enantiomers of the invention may be made by classical solution synthesis by the coupling of suitably protected (R)-histidine with another suitably protected amino acid. The cyclic dipeptide enantiomer

(R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione may be prepared, for example, by coupling N-benzoyloxycarbonyl-(R)-phenylalanine and (R)-histidine methyl ester in the presence of dicyclohexylcarbodiimide and benzotriazole to give N-benzoyloxycarbonyl-(R)-phenylalanyl-(R)-histidine methyl ester, removal of the N-benzoyloxycarbonyl protecting group by hydrogenation and cyclization.

The cyclic dipeptide enantiomers of formulae XII and XXXVI are, in general, crystalline solids and if they are crystallized from a solvent comprising water and/or an alcohol they may be in the form of hydrates or alcoholates and/or they may contain water or alcohol of crystallization.

In the process of the present invention the reaction between the aldehyde of formula II and hydrogen cyanide, in the presence of a cyclic dipeptide enantiomer catalyst, is preferably carried out in the presence of a solvent. The nature of the solvent is not narrowly critical but preferably it is a solvent in which the aldehyde of formula II and hydrogen cyanide are soluble. The cyclic dipeptide enantiomer catalyst may be soluble in the solvent, homogeneous catalysis, insoluble in the solvent, heterogeneous catalysis, or adsorb the solvent

swelling up to form a gel. Preferred solvents include inert hydrocarbons, halocarbons and halohydrocarbons which are solvents for the aldehyde of formula II and hydrogen cyanide and which are adsorbed by the catalyst to give a gel. Preferred solvents include the aromatic hydrocarbons such as, for example benzene, toluene and the xylenes.

5 One of the distinct advantages of the process of the present invention is that the cyclic dipeptide enantiomers of formulae XII and XXXVI may be recovered from the reaction mixture and reused. The cyclic dipeptide enantiomers may be recovered by treating the reaction mixture, or the residue after removal of the solvent from the reaction mixture, with a solvent, for example diethyl ether, in which the reaction product is soluble but in which the cyclic dipeptide enantiomer catalyst is insoluble. The catalyst may then be
10 recovered by filtration, recrystallised from water or an aqueous solvent, and dried. 10

The amount of the cyclic dipeptide enantiomer used as a catalyst in the process of the present invention is not narrowly critical but preferably falls within the range of from 10^{-1} to 10^{-6} moles per mole of the aldehyde of formula II.

Surprisingly, it has been found that the degree of hydration in the cyclic dipeptide enantiomers of
15 formulae XII and XXXVI is important to the effectiveness of the catalyst in the process of the present invention. Preferably the catalyst has a degree of hydration which enables it to swell in the solvent being used as reaction medium to form a gel. Catalysts which have too little or too much water of hydration apparently fail to swell in the reaction medium and do not efficiently catalyse the asymmetric addition of hydrogen cyanide to the aldehydes of formula II. In practice, it has been found preferable if the catalyst
20 contains between 0.5 and 1.5 moles, and more preferably 1 mole, of water of hydration or crystallization per mole of cyclic dipeptide enantiomer. 20

Also surprisingly, it has been found that the cyclic dipeptide enantiomers of formulae XII and XXXVI improve in stereospecificity of addition of hydrogen cyanide to aldehydes of formula II after their first use. Therefore preferably, the cyclic dipeptide enantiomers of formula XII and XXXVI have first been used,
25 recovered, recrystallized and dried to the preferred hydration level before use in the process of the present invention to prepare α -substituted- α -cyanomethyl alcohol enantiomers of formula I. 25

In the process of the present invention the reaction between the aldehyde of formula II and hydrogen cyanide in the presence of a cyclic dipeptide enantiomer catalyst is carried out at a temperature below ambient temperature in order to obtain the desired stereospecificity of addition. Preferably the temperature
30 is within the range from -20 to 10°C , more preferably at or below 0°C , and most preferably at or below -5°C . 30

The reaction time required for the process of the present invention depends to a large extent on the specific aldehyde of formula II, the specific catalyst and the solvent used. However, in general a reaction time of between 1 and 100 hours is suitable and a reaction time of between 10 and 30 hours is preferred.

In the process of the present invention it has been found that cyclic dipeptide enantiomers made from
35 (R)-amino acids catalyse the formation of (S)- α -substituted- α -cyanomethyl alcohol derivatives when the cyano group has a higher priority (according to the Cahn-Ingold-Prelog Rules c.f. R S Cahn, C K Ingold and V Prelog Angew Chem Int Ed (1966) 5, 385 or Comprehensive Organic Chemistry Vol 1 pp 16-18, Ed. Barton & Ollis, Pergamon Press 1979, ISBN 0-08-021313-8) than the α -substituent or conversely the stereochemically equivalent (R)-configuration when the cyano group has a lower priority than the α -substituent. Conversely, it
40 has been found that the cyclic dipeptide enantiomers made from (S)-amino acids catalyse the formation of (R)- α -substituted- α -cyanomethyl alcohol derivatives when the cyano group has higher Cahn-Ingold-Prelog priority than the α -substituent or conversely the stereochemically equivalent (S)-configuration when the cyano group has a lower priority than the α -substituent. Therefore, the process of the present invention is eminently suitable for the preparation of either (R)- or (S)- α -substituted- α -cyanomethyl alcohol derivatives of
45 formula I. 45

Certain of the compounds of formula I prepared according to the process of the present invention are novel compounds. Therefore, in yet a further embodiment the invention provides a compound of formula I wherein R^1 is a group of formula VIIb wherein R^{13} , R^{14} , R^{15} , R^{16} and R^{17} are as hereinbefore defined with the proviso that at least one of R^{13} , R^{14} , R^{15} , R^{16} and R^{17} is a substituent other than hydrogen.

50 Certain of the compounds of formula I are useful intermediates for the preparation of a range of pyrethroid pesticides of formula XV 50



wherein



is a pyrethrin acid moiety or a pyrethroid acid moiety.

haloalkenyl, C₂ to C₆ alkynyl, C₂ to C₆ haloalkenyl, C₁ to C₆ alkoxy, C₁ to C₆ alkylthio, C₁ to C₆ alkylsulfinyl, acyl, acyloxy, (C₁ to C₆ alkoxy)carbonyl, (C₂ to C₆ alkenyloxy)carbonyl, and (C₂ to C₆ alkynyloxy)carbonyl;

T is selected from oxygen and sulfur;

R³⁹ is selected from hydrogen, halogen, cyano, nitro and C₁ to C₆ alkyl;

5 m and n are independently selected from the integers 1 to 3;

the dotted line in formula XXV represents a double bond present at a position either conjugated with or non-conjugated with the ketone group (C=O);

R⁴⁰, R⁴¹ and R⁴² are independently selected from hydrogen, C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, halogen, acyl and acyloxy;

10 R⁴³ is selected from hydrogen and C₁ to C₆ alkyl;

W is selected from C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, C₂ to C₆ alkenyl, C₂ to C₆ haloalkenyl, C₂ to C₆ alkynyl, C₂ to C₆ haloalkynyl, C₁ to C₆ alkoxy, cyano and C₃ to C₇ cycloalkyl;

G is selected from hydrogen and fluorine;

Y is selected from the groups R⁴⁵R⁴⁶C=CR⁴⁴— and R⁴⁵R⁴⁶R⁴⁸C—CR⁴⁴R⁴⁷— wherein:

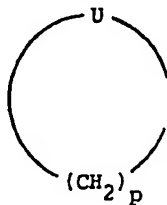
15 R⁴⁴ is selected from hydrogen and C₁ to C₆ alkyl;

R⁴⁵ is selected from hydrogen, halogen, C₁ to C₆ alkyl and C₁ to C₆ haloalkyl;

R⁴⁶ is selected from hydrogen, halogen, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, (C₁ to C₆ alkoxy) C₁ to C₆ alkyl, (C₂ to C₆ alkenyloxy) C₁ to C₆ alkyl, (C₂ to C₆ alkynyloxy) C₁ to C₆ alkyl, (C₁ to C₆ alkoxy)carbonyl, acyl, phenyl, phenyl substituted by halogen, nitro, cyano, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, C₁ to C₆ alkoxy or C₁ to C₆

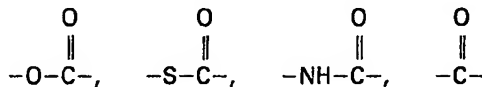
20 haloalkoxy, a substituent of the formula R⁵⁰R⁵¹C=CR⁴⁹— wherein R⁴⁹, R⁵⁰ and R⁵¹ are individually selected from hydrogen and C₁ to C₆ alkyl, and a substituent of the formula R⁵²ON=CH— wherein R⁵² is selected from hydrogen, C₁ to C₆ alkyl, C₂ to C₆ alkenyl and C₂ to C₆ alkynyl; or

R⁴⁵ and R⁴⁶ jointly form a cyclic group of formula XXVIII



XXVIII

35 wherein U is selected from the group —CH₂—,



and p is an integer selected from 2 to 5; and

R⁴⁷ and R⁴⁸ are independently selected from hydrogen and halogen;

R³² is selected from hydrogen and C₁ to C₆ alkyl;

45 R³⁰ and R³¹ are independently selected from hydrogen, halogen and C₁ to C₆ alkyl or R³⁰ and R³¹ jointly form an ethylene, trimethylene, tetramethylene or pentamethylene bridging group;

R³³ and R³⁴ are independently selected from hydrogen, C₁ to C₆ alkyl, halogen, phenyl, phenyl substituted by halogen, nitro, cyano, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl or C₁ to C₆ alkoxy, or R³³ and R³⁴ jointly form a bridging group selected from ethylene, trimethylene, tetramethylene, pentamethylene and groups of the

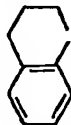
50 formulae



XXIX



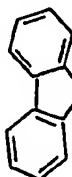
XXX



XXXI



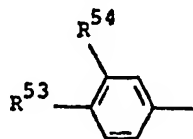
XXXII



XXXIII

Q is selected from C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl and the group

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XXXIV

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wherein:

R⁵³ is selected from hydrogen, C₁ to C₃ alkoxy, C₁ to C₃ alkylthio, C₁ to C₂ alkyl, nitro, fluoro, chloro, bromo and amino;

R⁵⁴ is selected from hydrogen and methyl; or

15 R⁵³ and R⁵⁴ jointly form a methylenedioxy bridging group.

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Examples of specific groups of formula J include those groups illustrated in Table 3 below:

TABLE 3

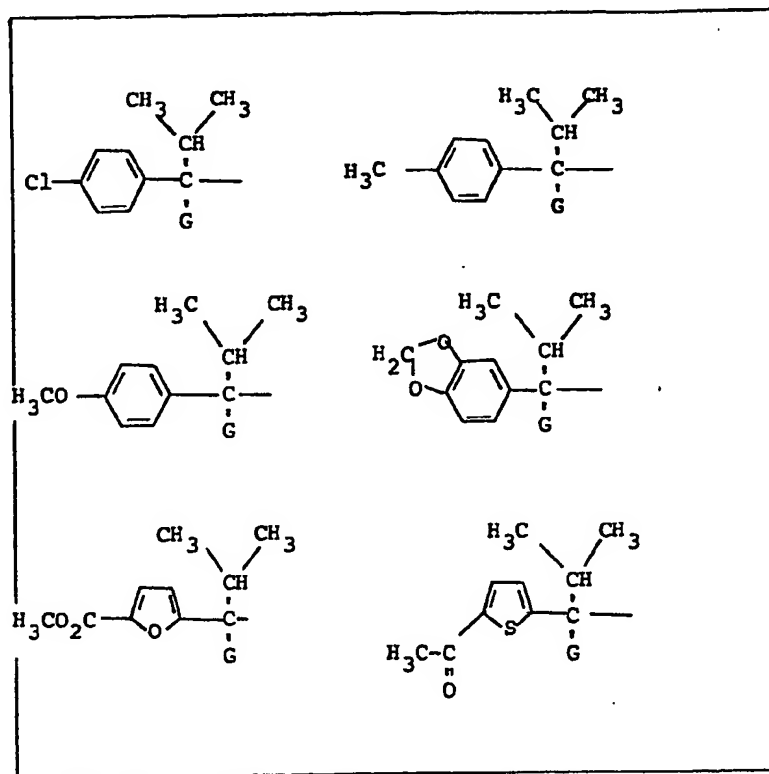


TABLE 3 - continued

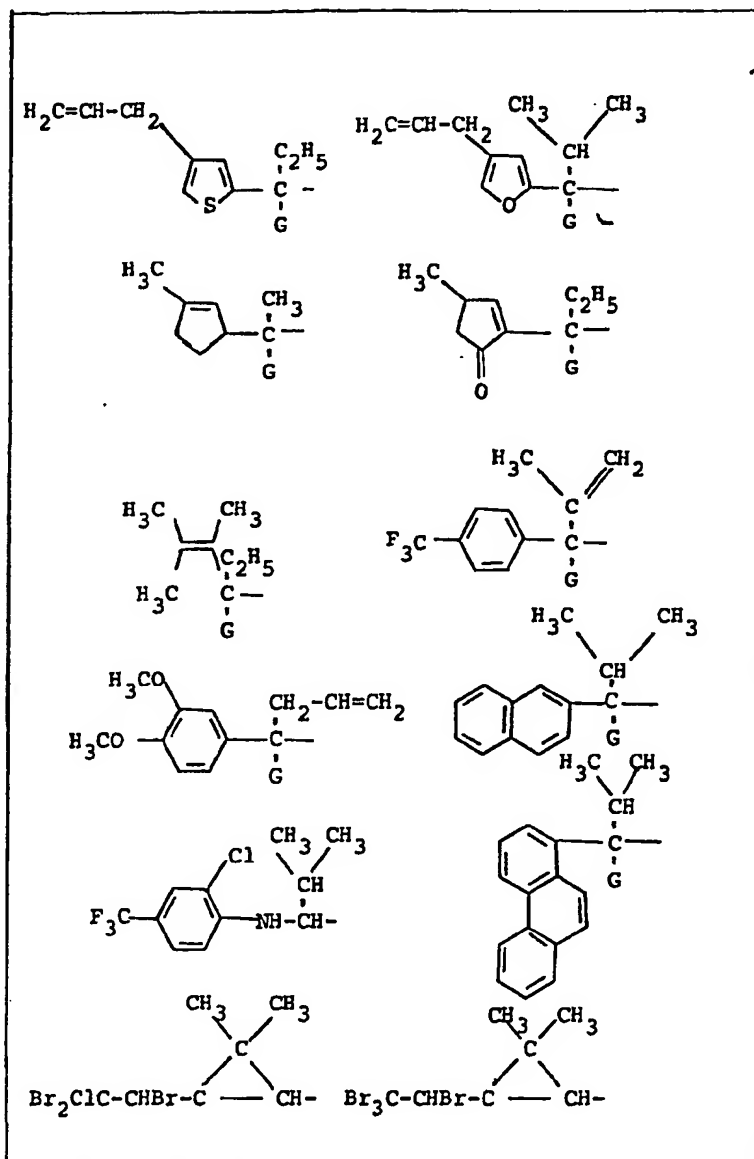


TABLE 3 - continued

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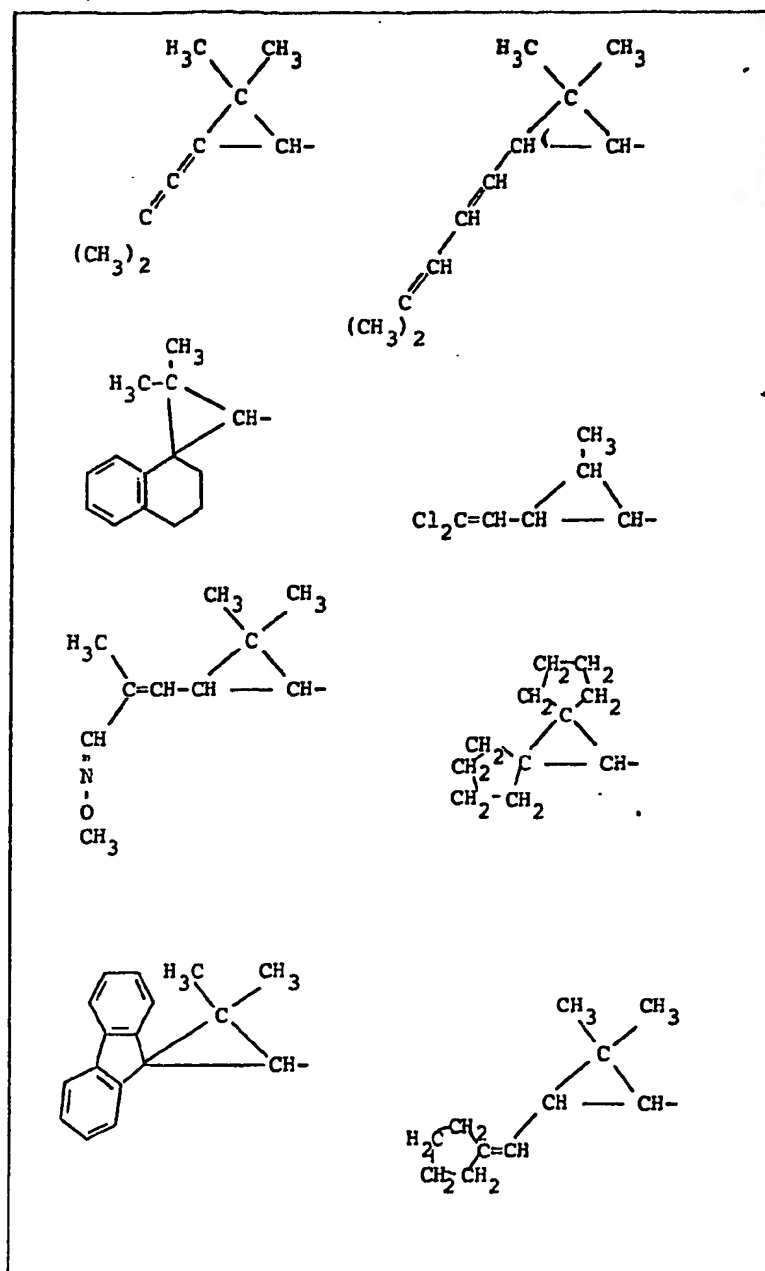
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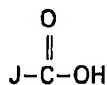
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50 Pyrethroids of formula XV may be prepared from the compounds of formula I by esterification. Accordingly in a further aspect, the invention provides a process for the preparation of a compound of formula XV which process comprises the esterification of an α -substituted- α -cyanomethyl alcohol enantiomer of formula I prepared as hereinbefore described, or a derivative thereof, with a pyrethrin acid or pyrethroid acid of formula XXXV

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XXXV

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wherein J is as hereinbefore defined, or a derivative thereof.

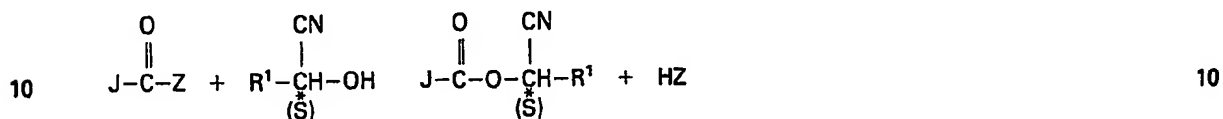
Preferably the α -substituted- α -cyanomethyl alcohol enantiomer of formula I prepared as hereinbefore described is selected from the group consisting of the enantiomers of:

65 α -cyano-3-phenoxybenzyl alcohol, α -cyano-4-fluoro-3-phenoxybenzyl alcohol,

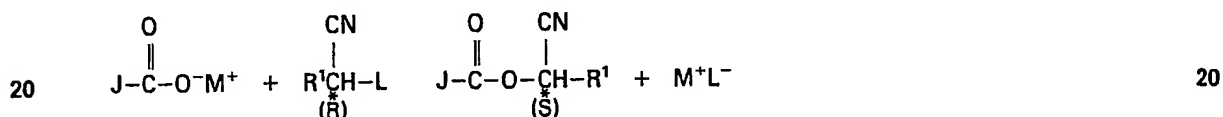
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3-(2,2-dichlorovinyl)- α -cyanobenzyl alcohol, α -cyano-pentafluorobenzyl alcohol, α -cyano- α -(6-phenoxy-2-pyridyl)methyl alcohol and α -cyano- α -(5-benzylfuryl)methyl alcohol, that is compounds no 1, 2, 4, 5, 3 and 6 respectively.

The esterification may involve the reaction of a pyrethrin acid, pyrethroid acid or derivative thereof, such as the corresponding acid halide, with an α -substituted- α -cyanomethyl alcohol enantiomer, with retention of configuration of the pyrethroid alcohol enantiomer, for example as shown below



Alternatively, the esterification may involve the reaction of a pyrethrin acid, pyrethroid acid or derivative thereof, such as the corresponding alkali metal salt, with an α -substituted- α -cyanomethyl alcohol derivative, for example a tosyl, mesyl or benzenesulfonyl derivative, with inversion of configuration of the pyrethroid alcohol enantiomer, for example as shown below



Specific examples of pyrethroids of formula XV which may be prepared from α -substituted- α -cyano-methyl alcohols of formula I prepared according to the process of the present invention include those compounds illustrated in Table 4 below.

TABLE 4

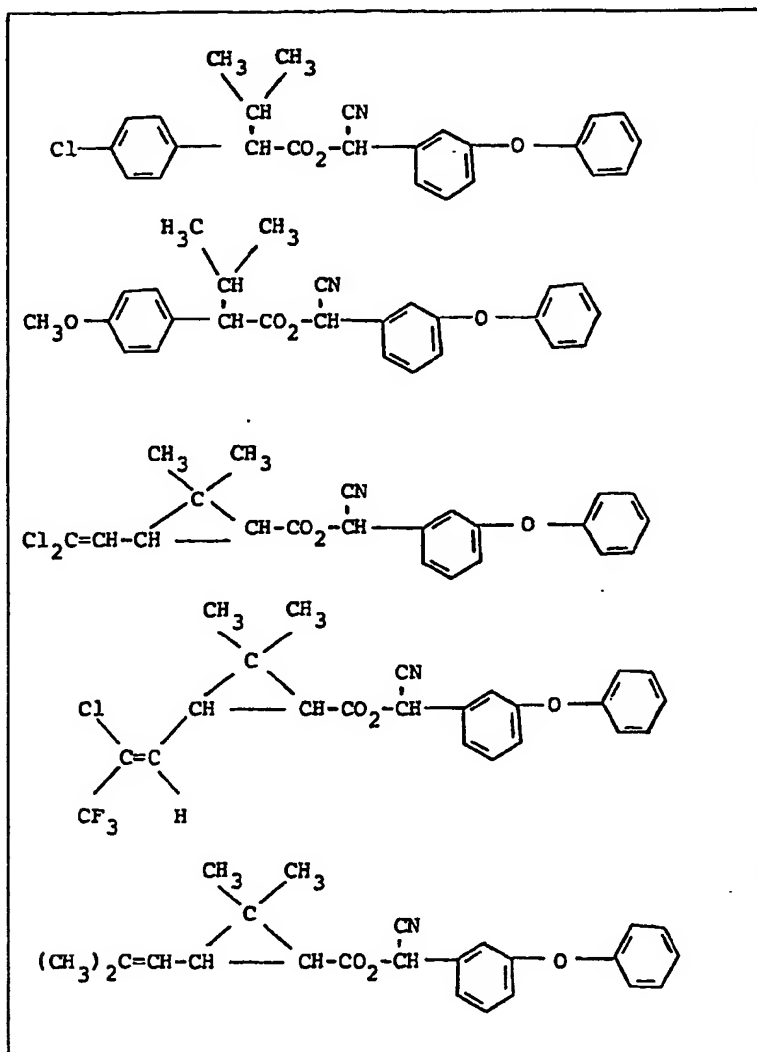


TABLE 4 - continued

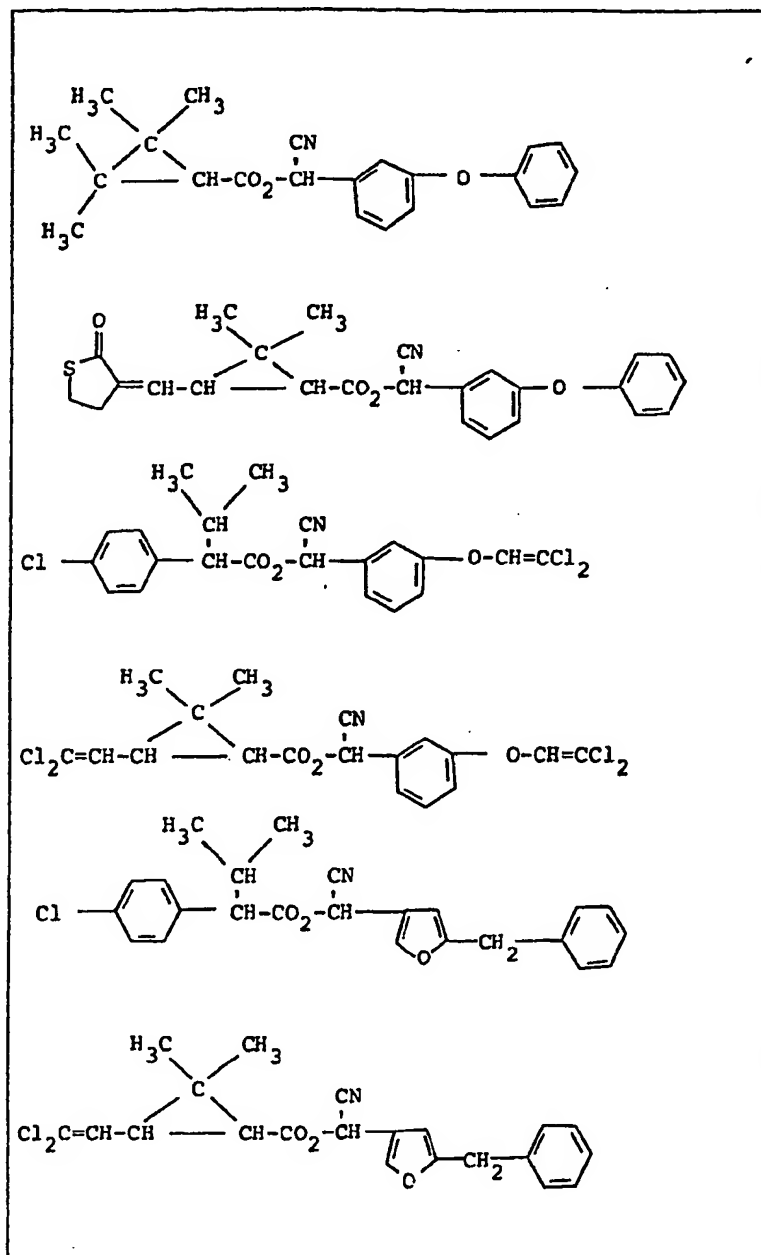


TABLE 4 - continued

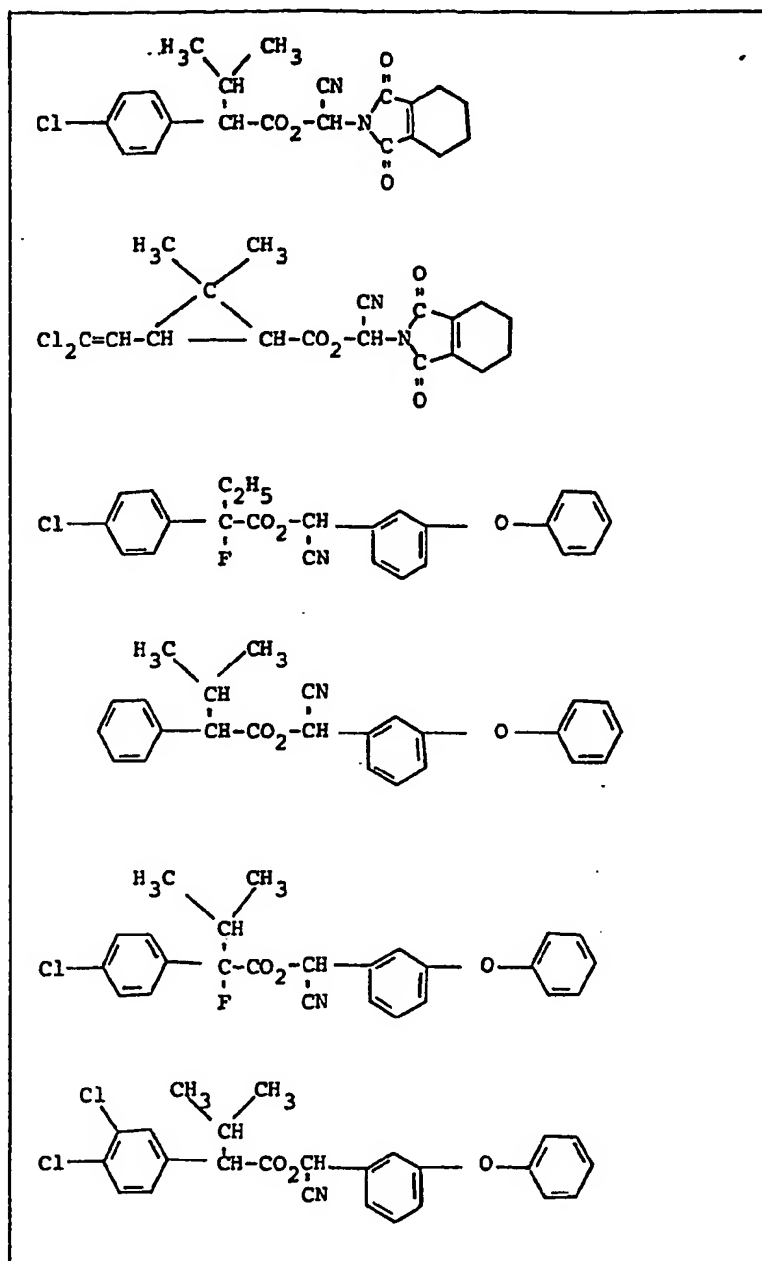


TABLE 4 - continued

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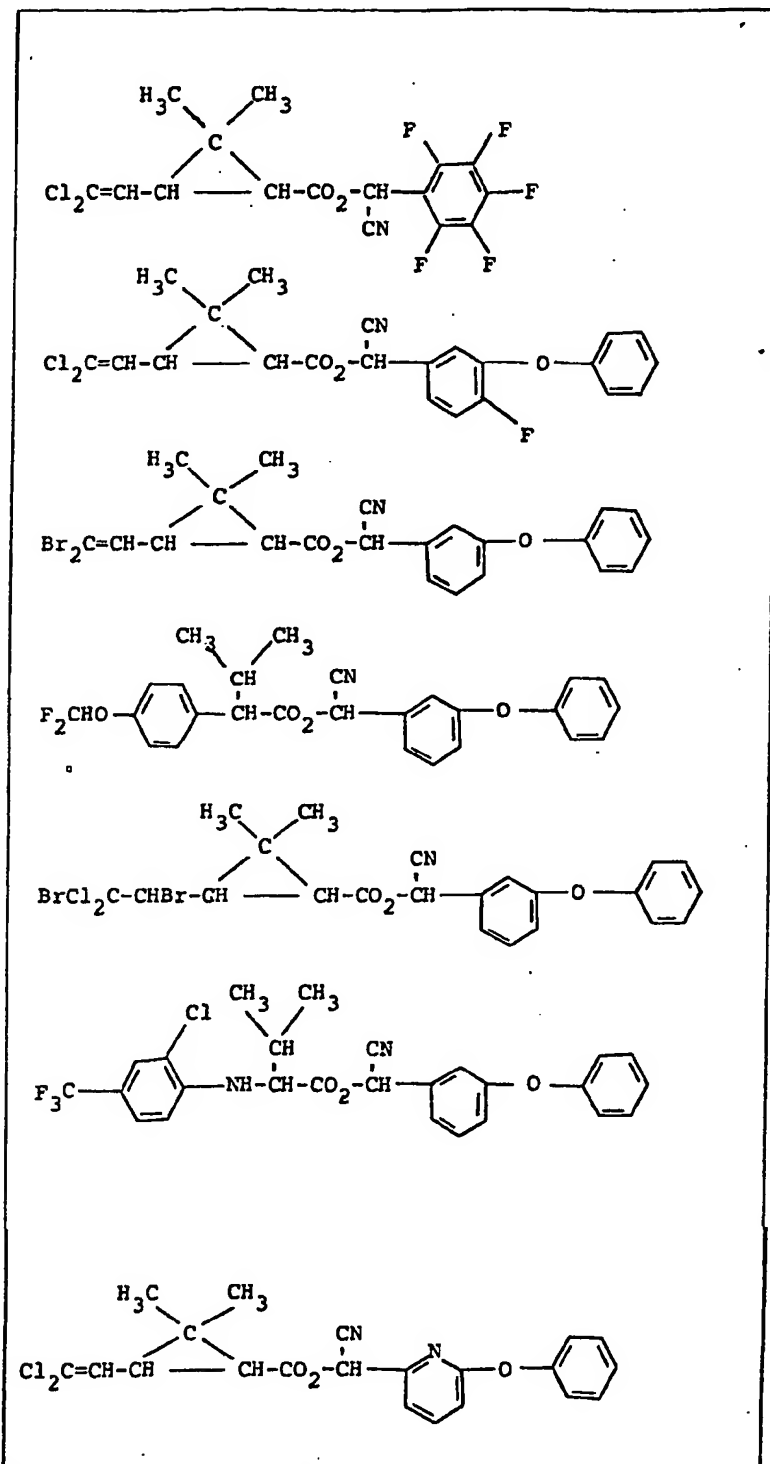
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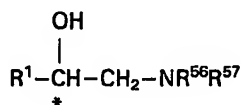
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Certain of the compounds of formula I are useful intermediates for the preparation of aryethanolamine enantiomers of formula XXXIX



wherein:

one of R⁵⁶ and R⁵⁷ is selected from hydrogen and the other is selected from the group consisting of

XXXIX

hydrogen, C₁ to C₆ alkyl and substituted C₁ to C₆ alkyl, or R⁵⁶ and R⁵⁷ together form a C₄ to C₆ alkylene linking group.

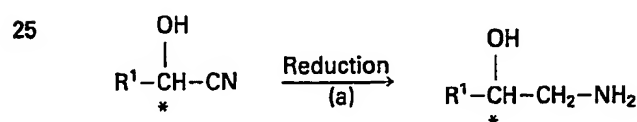
Among the preferred arylethanolamine enantiomers of formula XXXIX are those prepared from the novel compounds of formula I in which R¹ is a group of formula VIIb wherein R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are as
5 hereinbefore defined with the proviso that at least one of R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ is a substituent other than hydrogen.

Examples of suitable values for R⁵⁶ and R⁵⁷ include: hydrogen; C₁ to C₆ alkyl, and in particular, methyl, ethyl, isopropyl and tertiary butyl; and C₁ to C₆ substituted with phenyl and phenyl substituted with methyl, methoxy or hydroxy, with benzo-1,3-dioxanyl, or with octahydrodimethyldioxopuriny, and in particular,
10 1-(4-hydroxyphenyl)prop-2-yl, 2-(2-methoxyphenoxy)ethyl, 1-(benzo-1,3-dioxan-5-yl)-prop-2-yl, 1-(benzo-1,3-dioxan-5-yl)but-3-yl and 3-[3-(1,2,3,4,5,6,8,9-octahydro-7,9-dimethyl-2,8-dioxopuriny)propyl]; or R⁵⁶ and R⁵⁷ together form a C₄ to C₆ alkylene linking group, and in particular, pentamethylene.

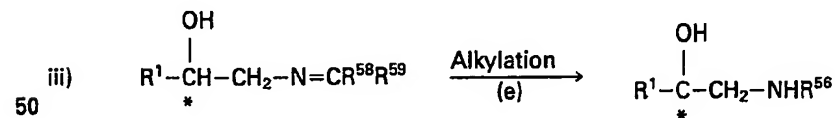
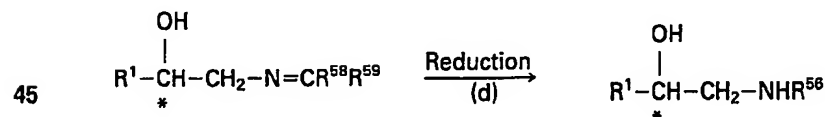
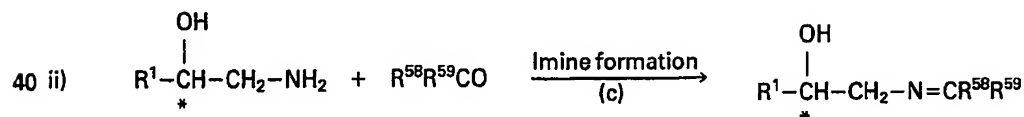
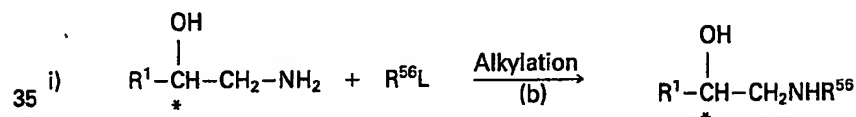
Arylethanolamine enantiomers of formula XXXIX may be prepared from the compounds of formula I by reduction and, optionally, N-alkylation. Accordingly in a still further embodiment the invention provides a
15 process for the preparation of a compound of formula XXXIX which process comprises the reduction of the nitrile group of an α-substituted-α-cyanomethyl alcohol enantiomer of formula I and, optionally, N-alkylation.

In the above process, the nitrile or cyano group may be reduced directly to an amino group and the amino group directly alkylated or reacted with an aldehyde or a ketone to form an imine and the imine either
20 reduced or alkylated as required to give a compound of formula XXXIX in which R⁵⁷ is hydrogen, as shown below wherein R⁵⁶L is an alkylating agent and R⁵⁸R⁵⁹C=O is an alkyl aldehyde or a dialkyl ketone.

Step 1



Step 2



The reduction of the nitrile group to an amino group shown in Step 1 (reaction a) above and the reduction of the imine group to an amino group shown in Step 2 ii) (reaction d) above may be carried out using any of
55 the procedures known in the art for the reduction of nitrile groups to amino groups and which will not racemize the chiral centre. Suitable reducing agents may be selected from sodium borohydride optionally complexed with cobalt chloride, boranetetrahydrofuran complex, lithium aluminium hydride, borane - dimethyl sulfide complex, sulfurated sodium borohydride, aluminium hydride in tetrahydrofuran, noble metal catalyst such as platinum or palladium optionally supported on carbon and Raney nickel.

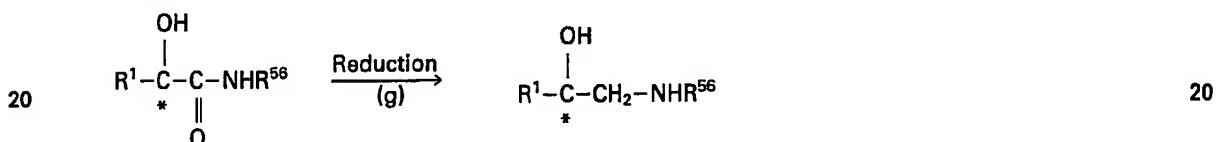
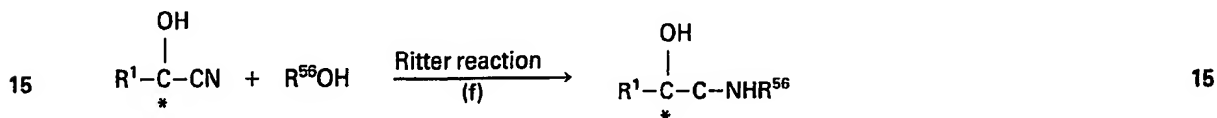
The alkylation of the amino group shown in Step 2 i) (reaction b) may be carried out using any of the
60 procedures known in the art for the N-alkylation of amines and which will not racemize the chiral centre. Suitable alkylating agents may be selected from compounds of formula R⁵⁶L in which L is a leaving group such as, for example, chloro, bromo or iodo.

The formation of the imine shown in Step 2 ii) (reaction c) may be carried out using any of the procedures
65 known in the art for the condensation of aldehydes or ketones with primary amines to form imines and

which will not racemize the chiral centre. It will be recognized by those skilled in the art that the imine formation shown in Step 2 ii) (reaction c) and reduction shown in Step 2 ii) (reaction d) may be combined in a one step reductive alkylation process.

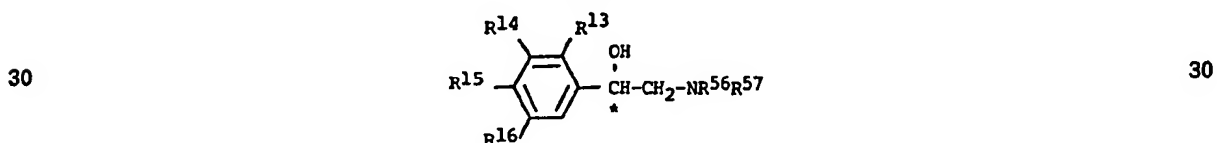
The alkylation of the imine shown in Step 2 iii) (reaction e) may be carried out using any of the procedures known in the art for the alkylation of imines and which will not racemize the chiral centre. Suitable alkylating agents may be chosen from alkyl Grignard reagents, alkyl cuprates and metal alkyls such as lithium alkyls, sodium alkyls and potassium alkyls.

In an alternative to reactions described above, the above process may be effected by reacting the nitrile or cyano group with an alcohol under Ritter reaction conditions known in the art to give an N-alkyl amide. The N-alkyl amide may then be reduced directly or converted to a thioamide and the thioamide to give a compound of formula XXXIX in which R⁵⁷ is hydrogen, as shown below.



Specific examples of aryethanolamine enantiomers of formula XXXIX which may be prepared from α -substituted- α -cyanomethyl alcohol enantiomers of formula I prepared according to the process of the present invention include those compounds illustrated in Table 5 below.

TABLE 5

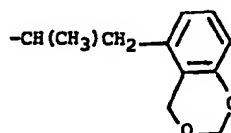


	Substituents						
	R ¹³	R ¹⁴	R ¹⁵	R ¹⁶	R ⁵⁶	R ⁵⁷	
	H	HO	H	H	H	H	
	H	HO	H	H	CH ₃	H	
40	H	HO	H	H	C ₂ H ₅	H	40
	H	HO	HO	H	H	H	
	H	HO	HO	H	CH ₃	H	
	H	HO	HO	H	C ₂ H ₅	H	
	H	HO	HO	H	CH(CH ₃) ₂	H	
45	H	HO	HO	H	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -	H	45
	H	HO	HO	H	a	H	
	H	HO	H	HO	-CH(CH ₃) ₂	H	
	H	HO	H	HO	-C(CH ₃) ₃	H	
	H	HO	H	HO	b	H	
50	H	HO	H	HO	c	H	50
	H	HOCH ₂	HO	H	-C(CH ₃) ₃	H	
	H	CH ₃ SO ₂ NH	HO	H	-CH(CH ₃) ₂	H	
	H	H	HO	H	H	H	
	H	H	HO	H	CH ₃	H	
55	H	H	HO	H	-(CH ₂) ₃ CH ₃	H	55
	H ₂ NCONH	HO	H	H	-C(CH ₃) ₃	H	
	H	Cl	H ₂ N	Cl	-C(CH ₃) ₃	H	
	Cl	H	H	H	-CH(CH ₃) ₂	H	
	H	CH ₃ O	HO	CH ₃ O	-CH ₃	H	
60	H	H ₂ NSO ₂	H ₃ C	H	d	H	60
	H	H	NO ₂	H	-CH(CH ₃) ₂	H	
	H	-CH=CH-CH=CH-		H	-CH(CH ₃) ₂	H	

Code:

5

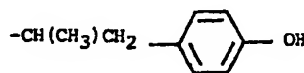
a -



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b -

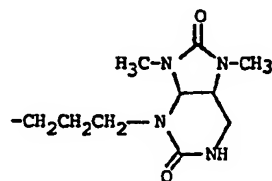


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c -

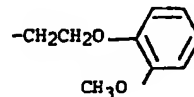


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d -



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Certain of the aryethanolamine enantiomers of formula XXXIX are believed to be novel compounds *per se*. Accordingly, in further aspects the invention provides novel enantiomers of formula XXXIX prepared from enantiomers of formula I prepared according to the process of the present invention.

The invention is now illustrated by, but in no way limited to, the following Examples.

40

EXAMPLE 1

Preparation of (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)2,5-piperazinedione

(i) (R)-phenylalanine (9.24 g; 0.056 mol) was dissolved in aqueous sodium hydroxide (28 cm³ of 2 M) and the solution was cooled to 0°C. Benzylchloroformate (8.8 cm³; 0.06 mol) and aqueous sodium hydroxide (15.3 cm³) were simultaneously added dropwise to the stirred solution over a period of 1 hour. The mixture was stirred at room temperature for 2.5 hours and then extracted with diethyl ether (100 cm³). The aqueous layer was separated and the pH adjusted to 2.0 by the dropwise addition of aqueous 2 M sulfuric acid. The acidified aqueous solution was extracted with ethyl acetate (2 x 50 cm³) and the combined organic extracts were dried over anhydrous sodium sulfate and the solvent evaporated. The solid residue was recrystallised from an ethyl acetate/hexane solvent mixture to give N-benzylloxycarbonyl-(R)-phenylalanine (14.09 g; 84%) as a crystalline solid mp 86-87° ([α]_D = -60.4°; C=0.00562 g/cm³; CHCl₃).

(ii) (R)-Histidine monohydrochloride monohydrate (5 g; 23.8 mmol) was suspended in methanol (150 cm³) and hydrogen chloride gas was bubbled through the stirred suspension over a period of 2 hours. The solution was heated under reflux for a period of one hour and then diethyl ether (150 cm³) was added to the solution. The precipitated solid was collected by filtration, washed with diethyl ether and dried to give (R)-histidine methyl ester dihydrochloride (5.6 g; 97%) as a solid mp 208-210°C ([α]_D = -7°; C=0.0025 g/cm³; H₂O).

(iii) A mixture of N-benzylloxycarbonyl-(R)-phenylalanine (2.67 g; 8.96 mmol), dicyclohexylcarbodiimide (1.84 g; 8.93 mmol), 1-hydroxybenzotriazole (1.20 g; 8.9 mmol) and acetonitrile (60 cm³) was stirred at a temperature of 0°C for a period of one hour. Triethylamine (1.8 g; 2.5 cm³; 18 mmol) was added to a suspension of (R)-histidine methyl ester dihydrochloride (2.17 g; 9 mmol) in acetonitrile (50 cm³) and the suspension was stirred for a period of three hours at room temperature. The (R)-histidine methyl ester mixture was added to the N-benzylloxycarbonyl-(R)-phenylalanine mixture and the resultant mixture was stirred at room temperature for a period of four hours. The precipitated solid was filtered off and the filtrate

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was evaporated to dryness. The residue was dissolved in chloroform (70 cm³) and the solution was washed with saturated aqueous sodium hydrogen carbonate solution (40 cm³) and then with water (40 cm³). The organic layer was dried over anhydrous sodium sulfate and the solvent evaporated. The residue was recrystallized from a dichloromethane/petroleum ether (bp 40-60°C) solvent mixture to give

- 5 N-benzoyloxycarbonyl-(R)-phenylalanyl-(R)-histidine methyl ester (3.0 g; 74%) as a crystalline solid mp 114-116°C ($[\alpha]_D = +12.7^\circ$; $c=0.0024$ g/cm³; CHCl₃). 5

- (iv) N-Benzoyloxycarbonyl-(R)-phenylalanyl-(R)-histidine methyl ester (2.95 g; 6.55 mmol) was dissolved in methanol (60 cm³), palladium - black catalyst (200 mg) was added and the solution was hydrogenated for a period of 6 hours. The catalyst was removed by filtration and the methanolic filtrate was heated under reflux for a period of 2 days. The solvent was evaporated and the residue was recrystallized from water to give 10 (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (1.12 g; 60%) as a crystalline solid mp 259-263° 10 (decomp.) ($[\alpha]_D = +74.7^\circ$; $C=0.0174$ g/cm³; CH₃COOH).

EXAMPLE 2

- 15 Preparation of (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione 15

- (i) (R)-Phenylalanine (1.65 g; 10 mmol) was dissolved in aqueous sodium hydroxide (5 cm³; 10 mmol of 2 M) and the solution was cooled to 0°C in an ice-bath. Benzoyloxycarbonyl chloride (1.9 g; 11 mmol) and aqueous sodium hydroxide (6 cm³; 12 mmol of 2 M) were simultaneously added to the stirred solution over a period of 15 minutes. The mixture was stirred at 0°C for a period of one hour and then at room temperature 20 for a period of 2.5 hours. The mixture was extracted with diethyl ether and the aqueous layer was separated 20 and adjusted to pH 2.0 by the dropwise addition of concentrated hydrochloric acid. The acidified aqueous mixture was extracted with chloroform and the organic extract was dried over anhydrous sodium sulfate and the solvent evaporated. The solid residue was recrystallized from a chloroform/petroleum ether solvent mixture to give N-benzoyloxycarbonyl-(R)-phenylalanine (2.69 g; 90% as a crystalline solid mp 87-89°C ($[\alpha]_D = -5.0$ 25 $C=0.01428$ g/cm³; C₂H₅OH). 25

- (ii) A solution of dicyclohexylcarbodiimide (2.1 g; 10 mmol) in ethyl acetate (10 cm³) was added dropwise to a stirred ice-cold mixture of N-benzoyloxycarbonyl-(R)-phenylalanine (3.0 g; 10 mmol), 4-nitrophenol (1.7 g; 12 mmol) and ethyl acetate (30 cm³). The mixture was stirred at a temperature of 0°C for a period of 30 minutes and then at room temperature for a period of 2.5 hours. The precipitated solid was filtered off and 30 the filtrate was concentrated to give a crystalline product which was recrystallized from ethanol to give 30 N-benzoyloxycarbonyl-(R)-phenylalanine 4-nitrophenyl ester (1.91 g; 45% as a white solid mp 120-123°C ($[\alpha]_D = +8.0$; $c=0.01627$ g/cm³; CHCl₃).

- (iii) A mixture of (R)-histidine monohydrochloride monohydrate (4.97 g; 24 mmole) and methanol (50 cm³) was stirred and heated under reflux for a period of one hour while dry hydrogen chloride gas was bubbled through the mixture. The mixture was then cooled in ice and the crystalline product was collected 35 by filtration, washed with diethyl ether and dried to give (R)-histidine methyl ester dihydrochloride (5.35 g; 93%) as a solid mp 208°C (decomp) ($[\alpha]_D = -9.6$; $C=0.01114$ g/cm³ H₂O). 35

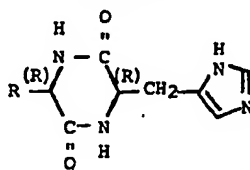
- (iv) (R)-Histidine methyl ester dihydrochloride (0.97 g; 4 mmol) was suspended in a mixture of acetonitrile (10 ml) and triethylamine (1.12 ml; 8 mmol) and the mixture was stirred at room temperature for a period of 5 hours. A suspension of N-benzoyloxycarbonyl-(R)-phenyl-alanine 4-nitrophenyl ester (1.68 g; 4 mmol) in acetonitrile (10 ml) was added and the mixture was stirred at room temperature for a period of 2 days. The solvent was evaporated and the solid was washed with diethyl ether and then dissolved in chloroform and the chloroform solution was washed twice with aqueous 10% ammonium hydroxide solution and then twice with water and dried over anhydrous sodium sulfate. The solvent was evaporated 45 and the residue was recrystallised from a dichloromethane/petroleum ether solvent mixture to give 45 N-benzoyloxycarbonyl-(R)-phenylalanyl-(R)-histidine methyl ester (1.27 g; 71%) as a crystalline solid mp 113-116°C ($[\alpha]_D = -13.2$; $C=0.00624$ g/cm³; MeOH).

- (v) N-Benzoyloxycarbonyl-(R)-phenylalanyl-(R)-histidine methyl ester (1.2 g; 2.7 mmol) was dissolved in methanol (50 cm³), freshly prepared palladium - black catalyst (300 mg) was added and the mixture was 50 hydrogenated for a period of 7 hours. The catalyst was removed by filtration and the filtrate was heated 50 under reflux for a period of 66 hours. The solvent was evaporated and the residue was recrystallized from water and the product dried overnight over phosphorous pentoxide to give (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (0.72 g; 96%) as a crystalline solid mp 276-278°C ($[\alpha]_D = +72.4$; $C=0.003$ g/cm³; CH₃COOH).

EXAMPLES 3 TO 9

The cyclic dipeptide enantiomers described in Table 6 below were prepared following essentially the same procedure as the described in Example 1 or Example 2 above.

TABLE 6



Example No	R	$[\alpha]_D$ in CH_3COOH (Conc. in g/cm^3)	mp $^{\circ}\text{C}$
3	$\text{C}_6\text{H}_5\text{CH}_2$	$+35^{\circ}$ (0.0092)	230-232 (decomp)
4	$4-\text{HOC}_6\text{H}_4\text{CH}_2$	$+48^{\circ}$ (0.0081)	268-270
5	$4-\text{C}_6\text{H}_5\text{CH}_2\text{OC}_6\text{H}_4\text{CH}_2$	$+59^{\circ}$ (0.016)	192-195
6	$4-\text{CH}_3\text{OC}_6\text{H}_4\text{CH}_2$	$+85^{\circ}$ (0.0014)	238-240
7*	$3-\text{FC}_6\text{H}_4\text{CH}_2$	$+55^{\circ}$ (0.0026)	270-285
8	C_6H_5	$+31^{\circ}$ (0.008)	265-270 (decomp)
9	CH_3	$+38^{\circ}$ (0.014)	249-250

*(R,S)-3-fluorophenylalanyl-(R)-histidine

EXAMPLE 10

Preparation of (R)- α -cyano-3-phenoxybenzyl alcohol

A mixture of (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione (0.06 g; 0.2 mmole) and benzene (4.0 cm^3) was cooled under nitrogen in an ice bath. 3-Phenoxybenzaldehyde (2.0 ml; 12 mmole) and then hydrogen cyanide (0.8 cm^3 ; 20 mmole) were rapidly added to the cooled, stirred mixture. The mixture was stirred for 19 hours by which time it had become clear.

The excess hydrogen cyanide and the benzene were removed by evaporation under reduced pressure to give an oil. Diethyl ether (20 cm^3) was added to the oil and the precipitated (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione was collected by filtration and washed thoroughly with diethyl ether (20 cm^3). The combined filtrate and washings were concentrated under reduced pressure to remove the solvent and give a pale yellow oil.

The oil was analysed by proton nuclear magnetic resonance spectroscopy and found to contain 83 mole percent α -cyano-3-phenoxybenzyl alcohol and 17 mole percent unreacted 3-phenoxybenzaldehyde. The optical rotation of the mixture ($[\alpha]^{34} = +12.0$; 3.54 g/dl; benzene), which, based on the optical rotation of (S)- α -cyano-3-phenoxybenzyl alcohol * ($[\alpha]_D^{20} = 16.5$; 0.008 g/ cm^3 ; benzene), after correction for the mole fraction of α -cyano-3-phenoxybenzyl alcohol in the product mixture, indicates that (R)- α -cyano-3-phenoxybenzyl alcohol had been formed in 73% enantiomeric excess.

*Reported in United Kingdom Patent Application No 2 013 670A

EXAMPLE 11

Preparation of (R)- α -cyano-3-phenoxybenzyl alcohol

The procedure described in Example 10 was repeated using a reaction time of 26 hours.

Proton nuclear magnetic resonance spectroscopic analysis of the product showed a 71 mole percent conversion and the optical rotation of the product ($[\alpha]_D^{34} = +11.7$; 0.0342 g/ cm^3 ; benzene) showed, after correction, that (R)- α -cyano-3-phenoxybenzyl alcohol had been formed in 71% enantiomeric excess.

EXAMPLE 12

Preparation of (R)- α -cyano-3-phenoxybenzyl alcohol

The (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione collected by filtration from the reactions described in Examples 10 and 11 was recrystallized from water and partially dried under vacuum until crusty and granular.

The procedure described in Example 10 was repeated using (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione recovered as described above and a reaction time of 16 hours.

Proton nuclear magnetic resonance spectroscopic analysis of the product showed an 86 mole% conversion and the optical rotation of the product ($[\alpha]_D^{34} = +12.0$; 0.02966 g/cm³; benzene) showed, after correction, that (R)- α -cyano-3-phenoxybenzyl alcohol had been formed in 75% enantiomeric excess. 5

EXAMPLE 13

Preparation of (R)- α -cyano-3-phenoxybenzyl alcohol

The procedure described in Example 10 was repeated using (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione recovered as described in Example 12, toluene as solvent, a reaction temperature of -10°C and a reaction time of 17.5 hours. 10

Proton nuclear magnetic resonance spectroscopic analysis of the product showed an 88 mole% conversion and the optical rotation of the product ($[\alpha]_D^{34} = +16.4$; 3.593 g/dl; benzene) showed, after correction, that (R)- α -cyano-3-phenoxybenzyl alcohol had been formed in 99% enantiomeric excess. 15

EXAMPLE 14

Preparation of (S)- α -cyano-3-phenoxybenzyl alcohol

A mixture of freshly prepared (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (0.64 g; 2.1 mmol) and toluene (40 ml) was cooled under nitrogen to a temperature of -10°C . 3-Phenoxybenzaldehyde (2.1 cm³; 126 mmol) and then hydrogen cyanide (6 cm³; 150 mmol) were rapidly added to the cooled, stirred mixture. The mixture was stirred for 18.5 hours at -10°C by which time it had become clear. 20

The excess hydrogen cyanide and the benzene were removed by evaporation under reduced pressure to give an oil. Diethyl ether (50 cm³) was added to the oil and the precipitated (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione was collected by filtration and washed thoroughly with diethyl ether (50 cm³). The combined filtrate and washings were concentrated under reduced pressure to remove the solvent and give a pale yellow oil. 25

The oil was analysed by proton nuclear magnetic resonance spectroscopy and found to contain 93 mole percent α -cyano-3-phenoxybenzyl alcohol and 7 mole percent unreacted 3-phenoxybenzaldehyde. The optical rotation of the mixture ($[\alpha]_D^{34} = 11.6^\circ$; 6.921 kg/m³; benzene), which, based on the optical rotation of (S)- α -cyano-3-phenoxybenzyl alcohol * ($[\alpha]_D^{20} = -16.5$; 0.008 g/cm³; benzene), after correction for the mole fraction of α -cyano-3-phenoxybenzyl alcohol in the product mixture, indicated that (S)- α -cyano-3-phenoxybenzyl alcohol had been formed in 70% enantiomeric excess. 30

*Reported in United Kingdom Patent Application No 2 013 670A

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EXAMPLES 15 TO 17

The procedure described in Example 14 above was repeated using recovered and recrystallised (see Example 12) (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione and the results are reported in Table 7 below. 40

TABLE 7

Example No	Reaction Time hours	Yield %	$[\alpha]_D$ (conc. in g/cm ³ solvent)	Enantiomeric Excess
15	19	84	-16.5 (0.0354/C ₆ H ₆)	100 ^a
16	19	84	-17.9 (0.0362/C ₆ H ₆)	108 ^a
16	19	84	-23.4 (0.0159/CCl ₄)	90 ^b
17	16	89	-26.1 (0.0192/CCl ₄)	99 ^b 89 ^c

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Code:

a - Enantiomeric excess based on the optical rotation reported in United Kingdom Patent Application 2 013 670A.

b - Enantiomer excess based on the optical rotation reported in Tetrahedron Letters (1984), 25, 591.

c - Calculated by converting the product alcohol into a pair of diastereo-isomers by esterification with an optically active acid of known optical purity, measuring the proton nuclear magnetic resonance spectrum of the product and integrating the benzylic proton (ie the proton at the chiral centre) which has a different chemical shift for the two different diastereo-isomers. 60

EXAMPLE 18

*Preparation of (S)- α -cyano-3-phenoxybenzyl (1R/S)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate (1R/S, 2R/S; 1 α *S-cyhalothrin)*

- 5 A solution of dicyclohexylcarbodiimide (0.13 g; 0.6 mmole) in dichloromethane (2 cm³) was added to a stirred solution of (1R/S)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-carboxylic acid (0.145 g; 0.6 mmole) and (S)- α -cyano-3-phenoxybenzyl alcohol (0.12 g; 0.5 mmole) in dry dichloromethane (3 cm³). The mixture was stirred overnight at room temperature, the dicyclohexylurea was filtered off and the filtrate was concentrated under reduced pressure. The residue was flash
10 chromatographed over silica gel (eluant benzene) and the first 40 cm³ of eluant was collected and the solvent removed by crystallization under reduced pressure to give 1R/S, 3R/S; 1 α *S-cyhalothrin 0.24 g as a golden oil. Optical rotation and/or proton nuclear magnetic resonance data is reported in Table 8 below. 10

EXAMPLES 19 TO 24

- 15 The following pyrethroids were prepared from the corresponding pyrethroid acid and (S)- α -cyano-3-phenoxybenzyl alcohol following essentially the same procedure as that described in Example 18. 15
- Example 19 – (S)- α -cyano-3-phenoxybenzyl (1R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcarboxylate (1R, 3R/S; 1 α *S-cyhalothrin). 20
- 20 Example 20 – (S)- α -cyano-3-phenoxybenzyl (1R)-cis-3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylate (deltamethrin). 20
- Example 21 – (S)- α -cyano-3-phenoxybenzyl (1R/S)-cis-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (1R/S; 1 α *S-cis-cypermethrin). 25
- 25 Example 22 – (S)- α -cyano-3-phenoxybenzyl (1R/S)-trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (1R/S; 1 α *S-trans-cypermethrin). 25
- Example 23 – (S)- α -cyano-3-phenoxybenzyl (1R/S)-cis/trans-3-[E/Z-2-chloro-2-(4-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (1 α *S-flumethrin). 30
- 30 Example 24 – (S)- α -cyano-3-phenoxybenzyl (2R/S)-2-(4-chlorophenyl)-3-methylbutanoate (2R/S; 1 α *S-fenvalerate). 30

Optical rotation and/or proton nuclear magnetic resonance data is reported in Table 8 below.

TABLE 8

5 *Physical data on synthetic pyrethroids prepared from (S)- α -cyano-3-phenoxybenzyl alcohol* 5

10	Example No	Appearance Melting Point °C	$[\alpha]_D$ in CHCl_3 (conc in g/cm^3)	Chemical Shift (ppm in CDCl_3)	10
	18	Oil	+10.1 (0.0093)	1.21-1.33 (6H,m); 1.98-2.25 (2H,m); 6.32, 6.38 (1H, 2xs)*; 6.84 (1H,d, J=9.1Hz); 6.98-7.48 (9H,m)	15
15	19	55-56	+35.7 (0.006)	1.21 (3H,s); 1.29 (3H,s); 1.98-2.28 (2H,m); 6.38 (1H,s); 6.83 (1H,d, J=8.8Hz); 6.97-7.45 (9H,m)	20
20	20	100-101	+16.9 (0.0066)	1.19 (3H,s); 1.24 (3H,s); 1.84-2.16 (2H,m); 6.37 (1H,s); 6.69 (1H,d, J=8Hz); 6.97-7.46 (9H,m)	25
25			+18.7 (0.0064)	1.21 (3H,d); 1.29 (3H,s); 1.84-2.34 (2H,m); 6.32, 6.36 (1H, 2xs)*; 6.17 (1H, d of d, J=8.5, 1.2 Hz); 6.98-7.45 (9H,m)	30
30	22	Oil	+4.8 (0.0066)	1.18, 1.22, 1.23, 1.33, (6H, 4xs); 1.65 (1H, d of d); 2.30 (1H,m); 6.37, 6.39 (1H,2xs)*; 5.60(1H,d of d, J=8.2, 2.0Hz); 6.98-7.56 (9H, m)	35
35	23	Oil	+3.0 (0.007)	1.13-1.39 (6H,m); 1.56-2.59 (2H,m); 6.34-6.60 (1H,m); 5.66-5.87 (1H, m); 6.97-7.40 (13H,m)	40
40	24	Oil	-1.4 (0.0051)	0.71 (3H,d of d); 1.00 (3H,m); 2.34 (1H,m) 3.22 (2H,d, J=10.2Hz); 6.3,6.34 (1H,2xs)*, 6.97-7.74 (13H,m).	45

50 *Multiplicity due to presence of diastereo-isomers.

EXAMPLE 25

Preparation of (R)- α -cyano- α -(2-naphthyl)methyl alcohol

55 A mixture of (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione (0.3 g; 0.1 mmole) and toluene (5 cm^3) was cooled under nitrogen to a temperature of -10°C . 2-Naphthaldehyde (0.80 g; 5 mmole) and then hydrogen cyanide (1.0 cm^3 ; 25 mmole) were rapidly added and the mixture was stirred at a temperature of -10°C for a period of 16 hours. Diethyl ether (25 cm^3) was added to the mixture to dissolve the cream coloured solid which had precipitated and to precipitate the dipeptide catalyst. The catalyst was removed by
60 filtration and the filtrate was concentrated under reduced pressure to give (R)- α -cyano- α -(2-naphthyl)methyl alcohol as a cream solid; mp (crude) $103-107^\circ\text{C}$; $[\alpha]_D = +16.0$ at a concentration of 0.00844 g/cm^3 in CHCl_3 .

EXAMPLES 26 TO 37

The following arylaldehydes were reacted with hydrogen cyanide either in the presence of (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione (code S,S) or (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione (code R,R) to produce the corresponding enantiomeric or enantiomer enriched α -aryl- α -cyano-methyl alcohol following essentially the same procedure as that described in Example 25.

TABLE 9

Example No	Aldehyde	Catalyst
26	3-methoxybenzaldehyde	S,S
27	4-methoxybenzaldehyde	S,S
28	4-trifluoromethylbenzaldehyde	S,S
29	2-methylbenzaldehyde	R,R
30	2-naphthaldehyde	R,R
31	3-chlorobenzaldehyde	R,R
32	3-acetyloxybenzaldehyde	S,S
33	3-nitrobenzaldehyde	S,S
34	3-benzyloxybenzaldehyde	R,R
35	3-hydroxybenzaldehyde	S,S
36	4-chlorobenzaldehyde	S,S
37	3,4-bis[1-(ethoxy)ethoxy]benzaldehyde	S,S

The results are reported in Table 10 below in which the Compound No refers to the α -aryl- α -cyano-methyl alcohols listed in Table 2.

TABLE 10

Example No	Product Compound No	Reaction Time Hours	Reaction Temp °C	Yield %	$[\alpha]_D$ (conc in g/cm ³)
26	21	16.5	-10	98	+25.5 (0.0241) ^a
27	22	26	-10	75	+25.9 (0.0271) ^b
28	23	16	-10	100	+6.7 (0.0337) ^a
29	35	19	-10	72	-12.7 (0.0157) ^a
30	24	16	-10	100	-23.5 (0.0048) ^a
31	25	21	-10	75	-17.7 (0.034) ^a
32	26	17	-10	90	+19.8 ^c (0.020) ^a
33	27	17	-10	95	+7.1 (0.024) ^a
34	29	21	-10	64	-7.2 (0.0124) ^b
35	9	16 ^d	-10	50	+12.9 (0.0174) ^e
36	30	17	-10	96	+15.9 (0.01545) ^e
37	33	17	-10	33	+6.1 (0.01345) ^a

60 Code:

a - $[\alpha]_D$ measured in CHCl₃

b - $[\alpha]_D$ measured in C₆H₆

c - Enantiomeric excess 74% (determined as described in Code c of Table 7.

d - Reaction run in a solvent mixture of 7 parts toluene to 3 parts tetrahydrofuran.

65 e - $[\alpha]_D$ measured in CH₃OH

EXAMPLE 38

Preparation of (R)-2-amino-1-(2-naphthyl)ethanol

A solution of (R)- α -cyano- α -(2-naphthyl)-methyl alcohol (0.37 g; 2 mmole; prepared as described in Example 25) in anhydrous diethyl ether (3 cm³) was added dropwise to a stirred suspension of lithium aluminium hydride (0.17 g; 4.5 mmole) in anhydrous diethyl ether (10 cm³). The mixture was heated under reflux for a period of 2 hours then cooled in an ice bath and water (1 cm³), 10% aqueous sodium hydroxide (2 cm³) and further water (2 cm³) were cautiously added. The organic layer was separated and the inorganic residue was washed several times with diethyl ether. The organic layer and etherial washings were combined, washed with water, dried over anhydrous sodium sulfate and the solvent was removed by evaporation under reduced pressure to give (R)-2-amino-1-(2-naphthyl)-ethanol as a white solid (0.33 g; 87%); mp (crude) 115-118°C; [α]_D (crude) = -23.0° (C.=0.00322 g/cm³ in EtOH).

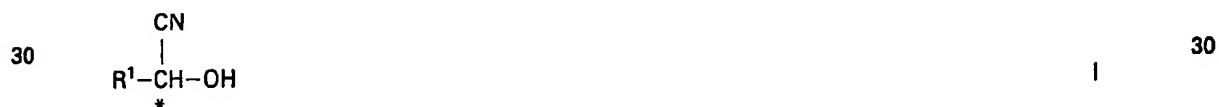
EXAMPLE 39

Preparation of (R)-2-(N-isopropylamino)-1-(2-naphthyl)-ethanol

A mixture of (R)-2-amino-1-(2-naphthyl)ethanol (0.08 g; 0.4 mmole; prepared as described in Example 38 above), acetone (10 cm³) and ethanol (10 cm³) was hydrogenated at room temperature and pressure for a period of 16 hours in the presence of platinum oxide. The platinum oxide catalyst was removed by filtration and the filtrate evaporated under reduced pressure to give a white solid. The residue was treated with aqueous 1M sodium hydroxide solution and the resulting mixture was extracted with diethyl ether. The organic extract was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give a white waxy solid. The solid was recrystallized from ethyl acetate to give (R)-2-(N-isopropylamino)-1-(2-naphthyl)ethanol as a white powder (0.09 g; 92%); mp 93-95°C; [α]_D = -45.0° (C.=0.00302 g/cm³ CHCl₃).

25 CLAIMS

1. A process for the preparation of an α -substituted- α -cyanomethyl alcohol enantiomer of formula I

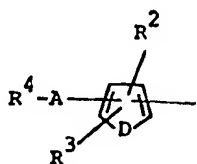


wherein the group R¹ is an alkenyl, alkynyl, aryl or heteroaryl group; which process comprises reacting an aldehyde of formula II

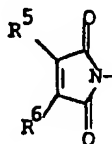


with hydrogen cyanide in the presence of a cyclic dipeptide enantiomer, and wherein said reaction is carried out at a temperature below ambient temperature.

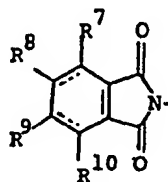
2. A process according to claim 1 wherein R¹ is selected from the groups consisting of:



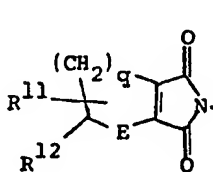
III



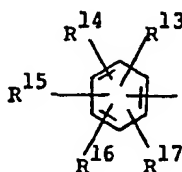
IV



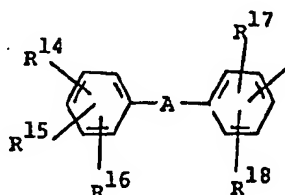
V



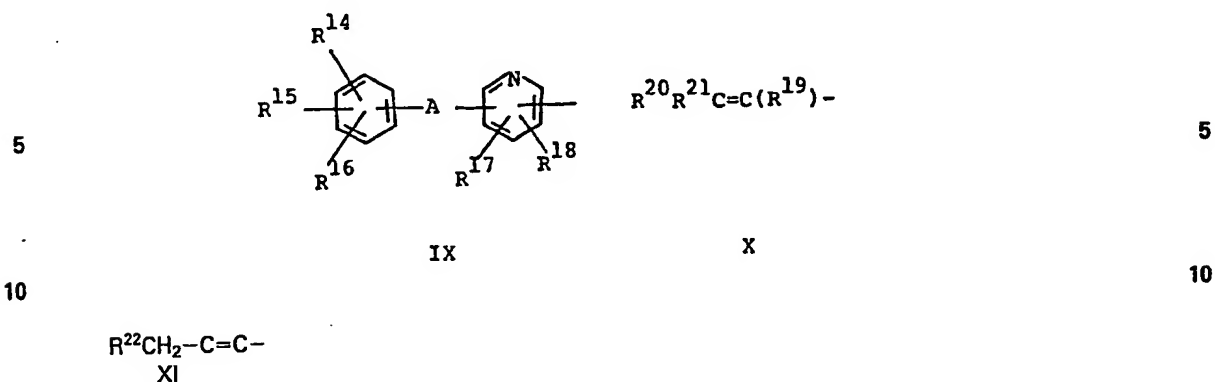
VI



VII



VIII



15 wherein:

R^2 and R^3 are independently selected from hydrogen, halogen, C_1 to C_6 alkyl and C_1 to C_6 haloalkyl, or R^2 and R^3 jointly form a trimethylene or tetramethylene bridging group;

A is selected from oxygen, sulfur, $-CO-$ and $-CH_2-$;

R^4 is selected from hydrogen, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, phenyl, furyl, thienyl and the groups phenyl, furyl and thienyl wherein each group is substituted by halogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxy or C_2 to C_6 alkenyl;

D is selected from oxygen and sulfur;

R^5 and R^6 are independently selected from C_1 to C_6 alkyl;

R^7 , R^8 , R^9 and R^{10} are independently selected from hydrogen, halogen, and C_1 to C_6 alkyl;

R^{11} and R^{12} are independently selected from hydrogen, C_1 to C_6 alkyl and halogen, or R^{11} and R^{12} jointly form a methylenedioxy bridging group;

E is selected from oxygen, sulfur and $-CH_2-$;

q is an integer selected from 1 and 2;

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are independently selected from the group consisting of: hydrogen; halogen; nitro; C_1 to C_6 alkyl; C_1 to C_6 haloalkyl; C_1 to C_6 hydroxyalkyl; C_2 to C_6 alkenyl; C_2 to C_6 alkynyl; C_1 to C_6 alkoxy; C_1 to C_6 alkylthio; (C_1 to C_6 alkoxy) carbonyl; benzyloxy, substituted benzyloxy; acyloxy; hydroxy; tri(C_1 to C_6 alkyl)silyloxy; (C_1 to C_6 alkoxy) C_1 to C_6 alkoxy; C_1 to C_6 alkoxy- C_1 to C_6 alkoxy; amino; N-(C_1 to C_6 alkyl)amino; N,N-di(C_1 to C_6 alkyl)amino; N-(C_1 to C_6 alkanoyl)amino; N-(C_1 to C_6 alkylsulfonyl)-amino; N-(benzenesulfonyl)amino; N-(substituted benzene-sulfonyl)amino; ureido; N-[tri(C_1 to C_6 alkyl)silyl]amino; sulfamoyl; N-(C_1 to C_6 alkyl)sulfamoyl; N,N-di(C_1 to C_6 alkyl)-sulfamoyl; carbamoyl; N-(C_1 to C_6 alkyl)carbamoyl; N,N-di(C_1 to C_6 alkyl)carbamoyl; C_1 to C_6 alkylsulfinyl; C_1 to C_6 alkylsulfonyl; thienyloxy; thenyl; furylmethyl; or two adjacent substituents are selected from the linking group buta-1,3-dienylene; and the groups $R^{24}R^{25}C=C(R^{23})O-$ and $R^{24}R^{25}C=C(R^{23})-$ in which R^{23} is selected from hydrogen and C_1 to C_6 alkyl and R^{24} and R^{25} are independently selected from hydrogen, halogen, C_1 to C_6 alkyl and C_1 to C_6 haloalkyl;

R^{19} is selected from hydrogen, chlorine and C_1 to C_6 alkyl;

R^{20} and R^{21} are independently selected from hydrogen, fluorine, chlorine, bromine, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, phenyl, benzyl, furylmethyl and thienylmethyl; and

R^{22} is selected from phenyl, phenoxy and the groups phenyl and phenoxy wherein each group is

substituted by halogen, nitro, cyano, C_1 to C_6 alkyl, C_1 to C_6 halo-alkyl or C_1 to C_6 alkoxy.

3. A process according to claim 2 wherein in the groups of formulae III, IV, V, VI, VII, VIII, IX, X and XI:

R^2 and R^3 are independently selected from hydrogen, halogen, C_1 to C_6 alkyl and C_1 to C_6 haloalkyl, or R^2 and R^3 jointly form a trimethylene or tetramethylene bridging group;

A is selected from oxygen, sulfur, $-CO-$ and $-CH_2-$;

R^4 is selected from hydrogen, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, phenyl, furyl, thienyl and the groups phenyl, furyl and thienyl wherein each group is substituted by halogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxy or C_2 to C_6 alkenyl;

D is selected from oxygen and sulfur;

R^5 and R^6 are independently selected from C_1 to C_6 alkyl;

R^7 , R^8 , R^9 , R^{10} are independently selected from hydrogen, halogen, and C_1 to C_6 alkyl;

R^{11} and R^{12} are independently selected from hydrogen, C_1 to C_6 alkyl and halogen, or R^{11} and R^{12} jointly form a methylenedioxy bridging group;

E is selected from oxygen, sulfur and $-CH_2-$;

q is an integer selected from 1 and 2;

R^{13} is selected from the group consisting of hydrogen, halogen, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, thienyloxy, thenyl, furylmethyl and the groups $R^{24}R^{25}C=C(R^{23})O-$ and $R^{24}R^{25}C=C(R^{23})-$ in which R^{23} is selected from hydrogen and C_1 to C_6 alkyl and R^{24} and R^{25} are independently selected from hydrogen, halogen, C_1 to C_6 alkyl and C_1 to C_6 haloalkyl;

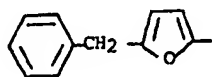
R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are independently selected from the group consisting of hydrogen, C_1 to C_6 alkyl, halogen and C_2 to C_6 alkenyl;

R^{19} is selected from hydrogen, chlorine and C_1 to C_6 alkyl;

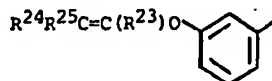
R^{20} and R^{21} are independently selected from hydrogen, fluorine, chlorine, bromine, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, phenyl, benzyl, furylmethyl and thienylmethyl; and

R^{22} is selected from phenyl, phenoxy and the groups phenyl and phenoxy wherein each group is substituted by halogen, nitro, cyano, C_1 to C_6 alkyl, C_1 to C_6 halo-alkyl or C_1 to C_6 alkoxy.

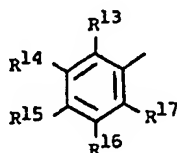
4. A process according to claim 1 or claim 2 wherein R^1 is selected from groups of the formulae



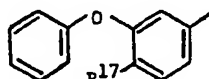
IIIa



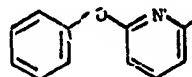
IIIb



VIIb



VIIIa



IXa

wherein:

in formula VIIIa, R^{17} is selected from hydrogen and halogen;

in formula VIIb, R^{13} , R^{14} , R^{15} , R^{16} and R^{17} are independently selected from the group consisting of hydrogen, halogen, nitro, hydroxy, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_1 to C_6 hydroxyalkyl, C_1 to C_6 alkoxy, (C_1 to C_6 alkoxy) C_1 to C_6 alkoxy, amino, N -(C_2 to C_6 alkanoyl)amino, N -(C_1 to C_6 alkylsulfonyl) amino, sulfamoyl, ureido, benzyloxy, benzoyloxy, or two adjacent substituents are selected from the linking group buta-1,3-dienylene; and in formula VIIa, R^{23} is hydrogen and R^{24} and R^{25} are independently selected from hydrogen and halogen.

5. A process according to claim 4 wherein:

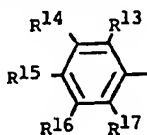
in formula VIIIa, R^{17} is selected from hydrogen and fluorine;

in formula VIIb, R^{13} , R^{14} , R^{15} , R^{16} and R^{17} are independently selected from the group consisting of hydrogen, halogen, methyl, trifluoromethyl, hydroxymethyl, methoxy, 1-(ethoxy)ethoxy, nitro, amino, acetamido, methanesulfonylamino, sulfamoyl, ureido, benzyloxy, benzoyloxy, or two adjacent substituents are selected from the linking group buta-1,3-dienylene;

in formula VIIa, R^{23} is hydrogen and R^{24} and R^{25} are independently selected from hydrogen and halogen.

6. A process according to any one of claims 1 to 5 inclusive for the preparation of a compound selected from (S)- α -cyano-3-phenoxybenzyl alcohol and (R)- α -cyano-3-phenoxybenzyl alcohol.

7. A process according to any one of claims 1, 2 and 4 to 5 inclusive for the preparation of a compound of formula I wherein R^1 is a group of formula VIIb



VIIb

wherein;

from one to three of the substituents R^{13} , R^{14} , R^{15} , R^{16} and R^{17} are selected from the group consisting of methoxy, methyl, halogen, hydroxy, nitro, trifluoromethyl, acetyloxy and benzyloxy, or two adjacent substituents are selected from the linking group buta-1,3-dienylene; and the remaining substituents are hydrogen.

8. A process according to any one of claims 1 to 7 inclusive wherein said cyclic dipeptide enantiomer comprises the residues of two amino acids selected from the group consisting of alanine, cysteine, histidine, homoserine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, phenylalanine, serine, thyronine, tryptophan, tyrosine, valine and derivatives thereof.

9. A process according to anyone of claims 1 to 8 inclusive wherein said cyclic dipeptide enantiomer comprises the residues of two amino acids one of which is selected from histidine and tryptophan and derivatives thereof and the other is selected from the group consisting of phenylalanine, thyronine, tyrosine, tryptophan, histidine and derivatives thereof.

10. A process according to any one of claims 1 to 9 inclusive wherein said cyclic dipeptide enantiomer is selected from (R)-3-benzyl-(R)-6-(4-imidazolylmethyl)-2,5-piperazinedione and (S)-3-benzyl-(S)-6-(4-imidazolylmethyl)-2,5-piperazinedione.

11. A process according to any one of claims 1 to 10 inclusive wherein said cyclic dipeptide enantiomer

comprises from 0.5 to 1.5 moles of water of hydration per mole of cyclic dipeptide enantiomer.

12. A process according to any one of claims 1 to 11 inclusive wherein said reaction is carried out in the presence of a solvent in which the aldehyde of formula II and hydrogen cyanide are soluble and which is adsorbed by the catalyst.

5 13. A process according to any one of claims 1 to 12 inclusive wherein said reaction is carried out at a temperature at or below 0°C. 5

14. A process according to any one of claims 1 to 13 inclusive wherein said reaction is carried out at a temperature below -5°C.

15. A process according to any one of claims 1 to 14 inclusive wherein said cyclic dipeptide enantiomer is present in an amount in the range of from 10^{-1} to 10^{-6} moles per mole of the aldehyde of formula II. 10

16. A cyclic dipeptide enantiomer comprising (R)-histidine or a derivative thereof as one of the amino acid residues.

17. A process for the preparation of a pyrethroid which process comprises the esterification of an α -substituted- α -cyanomethyl alcohol enantiomer of formula I prepared according to the process of any one of claims 1 to 15 inclusive with a pyrethrin acid or a pyrethroid acid or a derivative thereof. 15

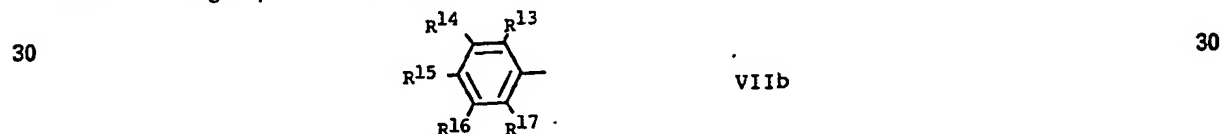
18. A process according to claim 17 wherein said α -substituted- α -cyanomethyl alcohol enantiomer is selected from the group consisting of the enantiomers of:

19. α -cyano-3-phenoxybenzyl alcohol, α -cyano-4-fluoro-3-phenoxybenzyl alcohol, 3-(2,2-dichlorovinyl)- α -cyanobenzyl alcohol, α -cyano-pentafluorobenzyl alcohol, 20 α -cyano- α -(6-phenoxy-2-pyridyl) methyl alcohol and α -cyano- α -(5-benzylfur-2-yl)methyl alcohol. 20

19. An α -substituted- α -cyanomethyl alcohol enantiomer of formula I



wherein R¹ is a group of formula VIIb



35 wherein: 35

R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are independently selected from the group consisting of hydrogen, halogen, nitro, hydroxy, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, C₁ to C₆ hydroxyalkyl, C₁ to C₆ alkoxy, (C₁ to C₆ alkoxy)C₁ to C₆ alkoxy, amino, N-(C₂ to C₆ alkanoyl)amino, N-(C₁ to C₆ alkylsulfonyl) amino, sulfamoyl, ureido, benzyloxy, benzoyloxy, or two adjacent substituents are selected from the linking group buta-1,3-dienylene; with the proviso that at least one of R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ is a substituent other than hydrogen. 40

20. A process for the preparation of an aryethanolamine enantiomer which process comprises the reduction of the nitrile group of an α -substituted- α -cyanomethyl alcohol enantiomer prepared according to any one of claims 1 to 15 inclusive and optionally alkylating the amino group so produced.

21. An aryethanolamine enantiomer whenever prepared from an α -cyanomethyl alcohol enantiomer prepared according to any one of claims 1 to 15 inclusive 45

22. A process as defined according to any one of claims 1 to 15 inclusive substantially as herein described with reference to any one of Examples 10 to 17 inclusive or 25 to 37 inclusive.

23. A cyclic dipeptide enantiomer as defined according to claim 16 substantially as herein described with reference to any one of Examples 1 to 9 inclusive.

24. A process as defined according to claim 17 or claim 18 substantially as herein described with reference to any one of Examples 18 to 24 inclusive. 50

25. An α -substituted- α -cyanomethyl alcohol enantiomer as defined according to claim 19 substantially as herein described with reference to any one of Examples 10 to 17 inclusive or 25 to 37 inclusive.

26. A process as defined according to claim 20 substantially as herein described with reference to Examples 38 or 39. 55

27. An aryethanolamine enantiomer as defined according to claim 20 substantially as herein described with reference to Example 38 or 39.

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